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(5)

No. 09-117

Supreme Court, U.S.
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In the Supreme Court of the United States

APOTEX, INC. and APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF FOR PETITIONERS

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RULE 29.6 STATEMENT

Petitioners hereby incorporate by reference the statement pursuant to Rule 29.6 included in the petition for a writ of certiorari.

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REPLY BRIEF FOR PETITIONERS

In making so much of the supposedly unpredictable aspects of the chemistry at issue, respondents ("Sanofi") advance in this Court the very legal proposition that petitioners ("Apotex") contend is erroneous and warrants further review. Ultimately respondents fail to grapple with petitioners' basic point: An obsessive focus on *outcomes* rather than the *obviousness of the path followed to reach a result* is starkly inconsistent with the approaches of the U.S. Patent and Trademark Office and other courts of appeals in an earlier era; contrary to sound patent policy; and in conflict with a century of this Court's case law culminating in *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007).

Respondents' lengthy brief seems concerned more than anything with calling attention to the sweat of Sanofi's brow. That sweat, however, is legally immaterial. It was already rewarded, moreover, with a valid earlier patent against which the later one at issue must be judged. The petition raises a recurring issue of profound importance, and it should be granted so this Court can clarify that *KSR*'s lessons apply with no less force in an "unpredictable art."[1]

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[1] Respondents point out that the PTO has agreed to conduct a reexamination proceeding for the '265 patent. BIO 18. In the past this Court has been entirely untroubled by the pendency of such a proceeding. See *eBay Inc.* v. *MercExchange L.L.C.*, 547 U.S. 388, 391 n.1 (2006). In this case, even if the PTO were to invalidate the '265 patent, a final decision to that effect would not issue for many years.

I. Respondents Defend the Erroneous View of the Courts Below That Any Element of Unpredictability Is Sufficient To Confer Patentability Even If an Approach Was "Obvious To Try."

A. Respondents halfheartedly say that Apotex is "unfair[]" to characterize the Federal Circuit's decision as saying that any aspect of unpredictability in an experiment is sufficient to patent the result. Br. in Opp. ("BIO") 26. But the district court clearly believed that "evidence of the fact that *any* property of clopidogrel bisulfate is unexpected . . . rebuts the presumption that clopidogrel bisulfate is obvious," Pet. App. 107a (emphasis added), and respondents defend the court's "conclu[sion] that *each*" one of the compound's supposedly unexpected properties "rebutted that prima facie case," BIO 16 (emphasis added).

The Federal Circuit obviously agreed. It is respondents who repeatedly call attention (BIO 16, 20, 26) to its justification for affirming: "[A] person of ordinary skill would not have had the *expectation* that separating the enantiomers would be *likely* to produce an isomer having [i] absolute stereoselectivity as to *both* [ii] the favorable antiplatelet activity *and* [iii] the unfavorable neurotoxicity." Pet App. 30a (emphasis and bracketed numbers added). In other words, a person of ordinary skill would not have bet all his chips on the precise eventual outcome, even though it was (as Sanofi concedes, BIO 6) within the known range of possible outcomes, see Pet. 4, and (as Sanofi does not really dispute, see BIO 8) there were good, *objective* reasons why someone would want to separate the enantiomers of PCR4099. See Pet. 16; Br. of *Amici Curiae* AARP et

al. 6. In requiring a demonstration that the *exact* outcome would have seemed "likely" – and not just within a likely *range* of desirable results motivating the experiment – the Federal Circuit set the bar for a § 103 challenge far too high.

Yet respondents have followed suit. They contend that "predictability [i]s an essential attribute" of obviousness. BIO 19. If (as respondents contend) predictability is *necessary* to invalidate a patent under § 103, then the contrapositive is also true: unpredictability – *any* unpredictability beyond the *de minimis* – must be sufficient to uphold it. Respondents and the Federal Circuit are both saying the same – erroneous – thing.

B. Respondents and the Federal Circuit have disregarded established legal principles. The petition explained that the proposition they advance – that an unexpected result trumps the obviousness of the path followed to reach it – clashes with this Court's prior decisions and with court of appeals decisions from before the creation of the Federal Circuit. Pet. 14-15; see, *e.g.*, *Ansonia Brass & Copper Co.* v. *Elec. Supply Co.*, 144 U.S. 11, 18 (1892) (the "application of an old process to a new and analogous purpose does not involve invention, even if the new result had not before been contemplated"); *Univ. of Ill. Found.* v. *Winegard Co.*, 402 F.2d 125, 127 (8th Cir. 1968) ("The statutory standard . . . is not 'predictability.' . . . Where logical exploration within known principles of the science achieves an unpredictable result, even though a commercially desirable one, the burden of nonobviousness is not necessarily overcome."); *Compton* v. *Metal Prods., Inc.*, 453 F.2d 38, 42 (4th Cir. 1971) ("'The ultimate question is whether a

hypothetical person having ordinary skill in the art would have readily found the same solution when addressing himself to the same problem.'").

Respondents have offered no response to this case law. And, although respondents try (at 2, 20) to divert attention from the on-point cases by citing *United States* v. *Adams*, 383 U.S. 39 (1966), that case is wholly inapposite given that the combination of elements at issue there was *not* obvious to try. See *id.* at 52 (certain "long-accepted factors, when taken together, would . . . deter any investigation into such a combination as is used by Adams").[2]

Astonishingly, Sanofi goes so far as to argue that *KSR* did not change the importance to the obviousness analysis of the "obvious to try" inquiry. BIO 27 ("*KSR* Did Not Reject the Principle that 'Obvious to Try' Is Generally Not the Standard for Obviousness."); contra 550 U.S. at 421-422 ("[T]he Court of Appeals . . . conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"). Sanofi's agenda is to limit *KSR* so that it applies only to mechanical combinations and not to combinations of "reaction conditions and

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[2] Sanofi also cites *Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273 (1976), and *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57 (1969), but those cases stand only for the proposition that a combination of familiar elements that "yields no more than one would expect from such an arrangement" is not patentable. BIO 20 (quoting *KSR*, 550 U.S. at 417). We do not quarrel with that principle. Rather, as the cases cited at Pet. 14-15 show, the circumstances of *Sakraida* and *Anderson's-Black Rock* are not the *only* circumstances in which a patent is invalid for obviousness.

reagents" in chemistry and other "unpredictable arts," BIO 5, 22, 29; see also pages 10-11, *infra*, but surely *KSR* is not so provincial.

C. The reason "neither lower court made any . . . factual finding," BIO 3, that Sanofi's winning experiment was "obvious to try" is that they believed that the issue was irrelevant. Pet. 9; Pet. App. 27a, 112a. Thus, in arguing (at 2, 3, 21) that the experiment was in fact not "obvious to try," respondents assume answers to the very *KSR*-mandated inquiry that the courts below refused to conduct: Was there a design need or other pressure to solve a problem and a finite number of potential solutions such that Sanofi's chemists had good reasons to test the limited and well-known "variety of procedures" and "choices of reaction conditions and reagents," BIO 5, in an effort to single out the winning combination? See Pet. 13.

Sanofi (at 21) finds it significant that the result of any given choice of reaction conditions and reagents was not predictable, but *KSR*'s reference to a finite number of "predictable solutions" cannot mean that the exact outcome of an experiment or series of experiments must be perfectly knowable in advance. (After all, an experiment whose result is truly known in advance is a pointless experiment.) Instead, *KSR* was surely referring to scenarios in which any person having ordinary skill in the art predictably would test the same *limited set of choices*. And *KSR* requires not, as Sanofi suggests, an absolute "assurance," BIO 21, 22, that two enantiomers can be successfully isolated, but rather only a reasonable "anticipat[ion]," 550 U.S. at 421, that this is true.

Likewise, as regards salt formation, see Pet. 5 n.1, 6-7 n.2, it may be true that a person of skill in the art

would not have bet that the bisulfate form of the salt would turn out to be the most useful one. See BIO 10-11, 23. That is very different, however, from saying that the prior art deterred the investigation, see *Adams*, 383 U.S. at 52, that led to the bisulfate salt. So long as the person of ordinary skill had reasons to test a given set of acids that included sulfuric acid – and that point seems undisputed[3] – obviousness should not be defeated by the supposed unexpectedness of the identity of the winning substance, or of its properties.

Ultimately, respondents' analytical flaw is to assume that an inability to predict which one of a manageable number of known possibilities will work (even if it is reasonably likely that *one* of them will work) makes it not obvious to try the full set of possibilities. That is not the law.

II. The Federal Circuit Is Intractably Inconsistent

Respondents say that our "cynical assertion that case outcomes 'depend in large part on who the panelists are' . . . do[es] not withstand a methodical review." BIO 27-28. Unfortunately, it does. The 13 modern Federal Circuit cases discussed by petitioners and respondents in this connection (including this

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[3] See Pet. App. 73a (explaining that "the approach taken at Sanofi" to the identification of a suitable salt – namely, testing a large array of acids on the FDA-approved list, including many strong acids like sulfuric acid – was the same approach that a person of ordinary skill in the art would have used); see also *id.* at 74a ("[A] person of ordinary skill in the art would have known that . . . sulfuric acid [was one of] the three strongest acids used in pharmaceutical salts.").

case)[4] are divided almost evenly between decisions upholding and decisions invalidating patents on obviousness grounds. Yet, among those cases, there is not a single vote by any of the three panelists below to invalidate a patent for obviousness. On the contrary, in the relevant universe of cases, those three judges have each consistently voted to uphold (or to reverse a district court's or a panel's invalidation of) every one of the multiple patents they have been faced with.

Respondents contend that the Federal Circuit has "consistently held" that "unexpected and unpredictable results . . . are not automatically conclusive." BIO 24. In support of that assertion they cite *Pfizer* (as well as *Süd-Chemie*, 554 F.3d at 1009, which merely cites *Pfizer*). BIO 24-25. In *Pfizer*, however, two of the judges who decided this case wanted to rehear and reverse the panel decision because, on facts very similar to those at issue here, the *Pfizer* panel found obviousness using the "obvious-to-try" analysis endorsed by *KSR* and ignored by the panel

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[4] See BIO 24-25, 27-28 and Pet. 18-20 & n.6, 24 n.9 (citing *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, reh'g denied, 488 F.3d 1377 (2007); *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350 (2007); *Süd Chemie, Inc.* v. *Multisorb Techs., Inc.*, 554 F.3d 1001 (2009); *Forest Labs., Inc.* v. *Ivax Pharms., Inc.*, 501 F.3d 1263 (2007); *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293 (2007), reh'g denied (Dec. 3, 2007); *In re Kubin*, 561 F.3d 1351 (2009); *Muniauction, Inc.* v. *Thomson Corp.*, 532 F.3d 1318 (2008); *Bayer Schering Pharma AG* v. *Barr Labs., Inc.*, 575 F.3d 1341 (2009); *Abbott Labs.* v. *Sandoz, Inc.*, 544 F.3d 1341 (2008); *Ortho-McNeil Pharm., Inc.* v. *Mylan Labs., Inc.*, 520 F.3d 1358 (2008)); *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286 (2006); *Procter & Gamble Co.* v. *Teva Pharms. USA, Inc.*, 566 F.3d 989 (2009)).

in this case. If this case and *Pfizer* had each been heard by the other's panel, each would have come out the other way. See Pet. 18-20.

These panel-dependent outcomes are possible only because some judges, like Sanofi (see BIO 22, 29), believe that *KSR*'s teachings on "obvious to try" apply differently or not at all in the so-called "unpredictable arts." We acknowledge that the Federal Circuit has sometimes gotten this issue right. It is impossible, however, to maintain seriously that there are not deep differences between Federal Circuit panels composed of different judges (and between the PTO and some Federal Circuit panels). Nor has the full Federal Circuit (which has had many opportunities to fix this situation) shown any inclination to reconcile its divergent cases. As we have explained, these inconsistencies create tremendous uncertainty in an area of the law where clarity and predictability are essential. See Pet. 20-21.

III. The Petition Raises A Public Policy Issue of Profound Importance

A. Respondents say that the '265 patent does not extend the monopoly on a patented compound already on the market. BIO 29. But that is exactly what it has done. The earlier '596 patent (whose validity is not disputed) claimed not just PCR4099 but its enantiomers and their salts. Pet. 5. It is undisputed that, even without the '265 patent, the earlier patent would have rewarded respondents with many profitable years of market exclusivity for Plavix. The only function of the '265 patent has been to extend Sanofi's monopoly by eight years, with no corresponding social benefit. See Pet. 16-17. As petitioners and their *amici* have explained, the economic and

medical consequences of gratuitously delaying generic competition in this fashion are gigantic. Br. of *Amici Curiae* AARP et al. 1-4, 10-13; Pet. 23, 24.

Sanofi attempts to justify this abuse by referring, mantra-like, to the "years of effort" and "tens of millions of dollars" it spent to develop the racemate. BIO 3-4, 7, 9, 23, 29-30. That is the same mistake that the Federal Circuit made, and it contributes to the necessity of further review. Pet. 21. As petitioners have pointed out (with no response from respondents), "sweat of the brow" is not and never has been the criterion for patentability. *Ibid.*

More fundamentally, the racemate and its enantiomers were already disclosed in (among other places) the prior-art '596 patent. See Pet. 6. The earlier investments were thus protected by the earlier patents. See Pet. 16, 21-22. Respondents seem to forget that the obviousness inquiry is whether "*the differences between the subject matter sought to be patented and the prior art* are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person having ordinary skill in the art." 35 U.S.C. § 103 (emphasis added). See also *Graham* v. *John Deere Co.*, 383 U.S. 1, 17 (1966) ("Under § 103, the scope and content of the prior art are to be determined; *differences between the prior art and the claims at issue are to be ascertained*; and the level of ordinary skill in the pertinent art resolved." (emphasis added)). The validity of the '265 patent properly turns not on the size of Sanofi's investment in research and development since the 1970s, but on whether, *given that PCR4099 and its enantiomers were already disclosed*, one of the enantiomers *in*

isolation would have been obvious within the meaning of § 103.

Respondents also lose sight of the fact that the obviousness inquiry is an objective one. The actions of Sanofi's own chemists (including how much time they spent on which experiments), and Sanofi's subjective characterizations of the difficulty of each experiment are beside the point. Cf. *KSR*, 550 U.S. at 420 ("The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art."). Just as "[p]atentability shall not be *negatived* by the manner in which the invention was made," 35 U.S.C. § 103 (emphasis added), so too "the manner in which the invention was made" cannot possibly *confer* patentability.

B. Sanofi implies (at 28-30) that *KSR*'s lessons somehow carry less force in the life and chemical sciences because "unpredictability here is the rule, not the exception." It is critical, however, to remember *KSR*'s bottom-line message: "As progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts." 550 U.S. at 427. See Pet. 15-17.

That message is no less applicable in the life and chemical sciences. Even in fields in which "unpredictability is the rule," there is such a thing as "ordinary innovation" and improvements that are "expected in the normal course." See Pet. 22-23. As the Federal Court of Australia recently explained in

ruling that the Australian counterpart of the '265 patent was obvious:

> Trial and error are normal, everyday parts of laboratory work and non-inventive laboratory experiments. That is what the hypothetical skilled worker in a laboratory does – *if the outcomes of experiments were known, there would be little point in doing them. That is the nature of everyday, non-inventive, research.*

Addendum, *infra*, 82 (emphasis added); see also *id.* at 19 ("Trial and error in the choice of salts involved non-inventive laboratory experiments."). The Australian court invalidated Sanofi's patent on clopidogrel bisulfate because it recognized what the Federal Circuit did not: Patents are not supposed to reward "normal, everyday" experimental work (the kind that yields "advances that would occur in the ordinary course," 550 U.S. at 419), even if aspects of that work are inherently unpredictable.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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OCTOBER 2009

ADDENDUM

FEDERAL COURT OF AUSTRALIA

Apotex Pty Ltd v Sanofi-Aventis [2009] FCAFC 134

PATENTS – application for revocation – validity – claim to *d*-enantiomer (clopidogrel), pharmaceutically acceptable salts and addition salts of *d*-enantiomer, pharmaceutical compositions containing *d*-enantiomer and a process for preparation of *d*-enantiomer – prior art patents describe and claim the racemate and the enantiomers process for obtaining enantiomers well known and non-inventive – whether disclosure of salts of the racemate discloses salts of the enantiomers – whether *d*-enantiomer novel – whether pharmaceutically acceptable salts and addition salts of the *d*-enantiomer novel – whether pharmaceutical compositions containing *d*-enantiomer novel – selection patents – whether claims obvious and lack inventive step – starting point for applying common general knowledge of skilled addressee – "problem and solution" approach – whether claims valid as a manner of manufacture

Patents Act 1990 (Cth), s 138(3)
Patents Act 1952 (Cth), s 40

Advanced Building Systems Pty Limited v Ramset Fasteners (Aust) Pty Limited (1998) 194 CLR 171 cited

Aktiebolaget Hässle v Alphapharm Pty Limited (2002) 212 CLR 411 considered

Apotex Pty Limited (formerly GenRx Pty Ltd) v Sanofi-Aventis (2008) 78 IPR 485 affirmed in part

Re Beecham Group Ltd's (Amoxycillin) Application [1980] 97 RPC 261 cited

Biogen Inc v Medeva plc (1996) 36 IPR 438 cited

Bristol-Myers Squibb Company v FH Faulding & Co Limited (2000) 97 FCR 524 cited

General Tire & Rubber Company v Firestone Tyre and Rubber Company Ltd (1971) 1A IPR 121 cited

Hill v Evans (1862) 1A IPR 1 considered

H Lundbeck A/S v Alphapharm Pty Ltd (2009) 81 IPR 228 considered

Re IG Farbenindustrie AG's Patents (1930) 47 RPC 289 cited

Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd (2008) 78 IPR 20 considered

Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2) (2007) 235 CLR 173 considered

Merck & Co Inc v Arrow Pharmaceuticals Ltd (2006) 154 FCR 31 cited

Minnesota Mining and Manufacturing Company v Beiersdorf (Australia) Limited (1980) 144 CLR 253 cited

National Research Development Corporation v Commissioner of Patents (1959) 102 CLR 252 cited

Nicaro Holdings Pty Limited v Martin Engineering Co (1990) 91 ALR 513 referred to

NV Philips Gloeilampenfabrieken v Mirabella International Pty Limited (1995) 183 CLR 655 cited

Olin Corporation v Super Cartridge Co Pty Ltd (1977) 180 CLR 236 cited

Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC (2008) 77 IPR 449 considered

Wellcome Foundation Limited v VR Laboratories (Aust) Proprietary Limited (1981) 148 CLR 262 cited

APOTEX PTY LTD (ACN 096 916 148) v SANOFI-AVENTIS, SANOFI-AVENTIS US LLC and BRISTOL-MYERS SQUIBB INVEST CO LLC

NSD 1311 of 2008

SANOFI-AVENTIS, SANOFI-AVENTIS US LLC and BRISTOL-MYERS SQUIBB INVESTCO LLC v SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)

NSD 1408 of 2008

EMMETT, BENNETT & MIDDLETON JJ
29 SEPTEMBER 2009
SYDNEY

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN:	**APOTEX PTY LTD (ACN 096 916 148) Appellant**
AND:	**SANOFI-AVENTIS First Respondent**
	SANOFI-AVENTIS US LLC Second Respondent
	BRISTOL-MYERS SQUIBB INVEST CO LLC Third Respondent
JUDGES:	**EMMETT, BENNETT & MIDDLETON JJ**
DATE OF ORDER:	**29 SEPTEMBER 2009**

WHERE MADE: SYDNEY

THE COURT DIRECTS THAT:

1. The parties consult and submit jointly agreed proposed orders (including as to costs) to give effect to these reasons by 6 October 2009 or, if the parties are unable to agree on proposed orders, each party submit proposed orders by 6 October 2009.

Note: Settlement and entry of orders is dealt with in Order 36 of the Federal Court Rules. The text of entered orders can be located using eSearch on the Court's website.

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION NSD 1408 of 2008

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN:	**SANOFI-AVENTIS** **First Appellant**
	SANOFI-AVENTIS US LLC **Second Appellant**
	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**

JUDGES: **EMMETT, BENNETT & MIDDLETON JJ**

DATE OF ORDER: **29 SEPTEMBER 2009**

WHERE MADE: **SYDNEY**

THE COURT ORDERS THAT:

1. The parties consult and submit jointly agreed proposed orders (including as to costs) to give effect to these reasons by 6 October 2009 or, if the parties are unable to agree on proposed orders, each party submit proposed orders by 6 October 2009.

Note: Settlement and entry of orders is dealt with in Order 36 of the Federal Court Rules. The text of entered orders can be located using eSearch on the Court's website.

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN: **APOTEX PTY LTD (ACN 096 916 148)**
Appellant

AND: **SANOFI-AVENTIS**
First Respondent

SANOFI-AVENTIS US LLC
Second Respondent

BRISTOL-MYERS SQUIBB INVEST CO LLC
Third Respondent

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1408 of 2008**

BETWEEN:	**SANOFI-AVENTIS** **First Appellant**
	SANOFI-AVENTIS US LLC **Second Appellant**
	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**
JUDGES:	**EMMETT, BENNETT & MIDDLETON JJ**
DATE:	**29 SEPTEMBER 2009**
PLACE:	**SYDNEY**

REASONS FOR JUDGMENT

EMMETT J

INTRODUCTION

1 These two appeals are concerned with the validity of Australian Patent Number 597784 (**the Patent**), which is registered in the name of Sanofi-Aventis (**Sanofi**). Sanofi-Aventis US LLC (**Sanofi US**) and Bristol-Myer Squidd Invest Co

LLC (**Bristol-Myers**) are licensees of the Patent, as members of the Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (**the Partnership**). The Patent relates to a series of products and processes principally concerned with the compound consisting of one of the enantiomers of a racemate compound designated PCR 4099 (**PCR 4099**). The enantiomer in question (**the d-enantiomer**) has the international non-proprietary name Clopidogrel.

2 PCR 4099 was disclosed and claimed in Australian Patent Number 554358 (**the Australian 4099 Patent**). The Australian 4099 Patent, which is also registered in the name of Sanofi, relates to new thieno (3, 2-c) pyridine derivatives, their process of preparation and their therapeutic application in inhibiting thrombosis or clot formation in blood.

3 Apotex Pty Limited (**Apotex**) commenced a proceeding in the Court claiming an order that the Patent and all claims of the Patent be revoked (**the Apotex Proceeding**). Sanofi and the Partnership filed a cross-claim in that proceeding seeking orders restraining Apotex from infringing the Patent. Subsequently, Spirit Pharmaceuticals Pty Ltd (**Spirit**) also commenced a proceeding in the Court seeking revocation of the Patent (**the Spirit Proceeding**). The Apotex Proceeding, including the cross-claim, and the Spirit Proceeding were heard together and on 19 August 2008 a judge of the Court made orders in both proceedings.

4 The Patent has eleven Claims. The primary judge held that Claim 1 and Claims 6 to 11 were invalid. His Honour concluded that Claim 1 is invalid on the ground of lack of novelty and that Claims 10 and 11, as presently framed, fall with Claim 1. His Honour also held that Claims 6 to 9 were invalid on the ground of lack of inventive step. However, his Honour rejected all other grounds of invalidity in relation to those Claims and rejected all grounds of invalidity in respect of Claims 2 to 5. Accordingly, his Honour found that Claims 2 to 5 are valid.

5 On 19 August 2008, Apotex filed a notice of appeal (**the Apotex Appeal**) from certain of the orders made by the primary judge in the Apotex Proceeding and, on 8 September 2008 Sanofi and the Partnership filed a notice of cross-appeal (**the Cross Appeal**) from other orders made by the primary judge in that proceeding. On the same day, Sanofi and the Partnership filed a notice of appeal (**the Sanofi Appeal**) from orders made in the Spirit Proceeding.

6 In the Apotex Appeal, Apotex appeals from so much of the orders of the primary judge as failed to determine that Claims 2 to 5 are invalid. In the Cross Appeal and in the Sanofi Appeal, Sanofi and the Partnership appeal from the orders of the primary judge revoking Claim 1 and Claims 6 to 11. Spirit is the respondent in the Sanofi Appeal and supports the position adopted by Apotex in relation to each of the Claims. It has also filed notice of contention seeking to support the determinations of the primary judge in the Spirit Proceeding on different grounds.

THE CHEMISTRY

7 I have taken the following brief description of the relevant chemistry from the reasons of the primary judge. The parties did not suggest that there was any relevant inaccuracy in his Honour's findings.

8 The claimed invention of the Patent relates to organic chemistry, which is concerned with the study of carbon compounds and, in particular, with the **stereochemistry** of carbon compounds in relation to the three dimensional structure of their molecules. **Isomers** are compounds whose molecules consist of the same number and kind of atoms but differ in their structure or arrangement. Some compounds are said to be **optically active**. The means of identifying compounds that have such a property is to shine a plane of polarised light through a sample of the compound dissolved in an appropriate solvent. The extent of the rotation is then measured. Display of optical activity by a compound indicates that the chemical structure of a molecule of that compound is non-superimposable on its mirror image. That property is called **chirality** and the molecule is described as **chiral**. An organic compound is said to have a **chiral centre** if it includes a carbon atom bonded to four different substitutes.

9 Where there is optical activity, there are two, and only two, isomers, called **enantiomers**. The enantiomers differ in structure such that the arrangements of their atoms in space are non-superimposable mirror images of each other.

Enantiomers have identical physical and chemical properties except in two important respects. First, they rotate the plane of polarised light in opposite directions, though to the same extent. Secondly, they interact in different ways with other chiral compounds, including reacting with them at different rates. The isomer that rotates the plane of polarised light to the left, or counter-clockwise, is called the levo isomer or levo-rotary or l-enantiomer, and is designated (-). The other isomer, which rotates the plane of polarised light to the right, or clockwise, is called the dextro isomer, or dextro-rotary or d-enantiomer, and is designated (+).

10 A pure compound is always optically active if it is composed of chiral molecules. However, a mixture of equal amounts of enantiomers of the same compound will be optically inactive, since the equal and opposite rotations of the two enantiomers cancel each other out. A mixture comprised of equal amounts of the two enantiomers is called a **racemate** or a **racemic mixture** and is often designated by the prefix (+/-). The separation of a racemic mixture into its two optically active enantiomers is called **resolution**. The chemical formula of each enantiomer and of their racemic mixture is the same.

11 The salt of a chemical compound can be formed by combining an acid with a base. An acidic compound is characterised by its ability to donate a proton to its surroundings whereas a basic compound is characterised by its ability to

accept a proton from its surroundings. Salts may form a crystalline compound.

12 The **pharmacological** properties of a compound are concerned with the operation of the compound in a biological system *in vivo*. That involves the efficacy, tolerance and toxicity of the compound as a pharmaceutical drug. The claimed invention of the Patent is applied to biological systems, which are composed of chiral molecules. Because enantiomers interact with other chiral molecules in different ways, they will often behave differently in a biological system. That can result in the enantiomers having different physiological effects, manifested in the efficacy, tolerance and toxicity of the compound as a pharmaceutical drug.

THE PATENT AND ITS CLAIMS

13 The claimed invention of the Patent is primarily Clopidogrel. After obtaining regulatory approval, Sanofi launched a product under the name Plavix in 1998. The active ingredient of Plavix is the bisulphate salt of Clopidogrel. Plavix has been commercially successful. It inhibits platelet aggregation in the site of blood vessel damage, and so inhibits thrombosis or clot formation.

14 Claim 1 of the Patent is for the d-enantiomer of PCR 4099, namely, Clopidogrel. The l-enantiomer is said to be inactive and less well tolerated than the d-enantiomer. The claimed invention also relates to salts of the d-enantiomer produced by the addition of a pharmaceutically

acceptable mineral or organic acid. Thus, Claim 1 is for the d-enantiomer and its pharmaceutically acceptable salts and Claims 2, 3, 4 and 5 are respectively for the hydrochloride salt, the hydrogen sulfate or bisulphate salt, the hydrobromide salt and the taurocholate salt.

15 The specification of the Patent says that the d-enantiomer can be prepared by forming the salt of PCR 4099 with an optically active acid in a solvent, repeated crystallisations of the salt until a product of constant optical rotatory power is obtained, followed by the liberation of the d-enantiomer from its salt by a base. If required, a salt is formed between the d-enantiomer and a pharmaceutically acceptable acid. That process is the subject of Claim 6. Claim 7 is for the process described in Claim 6 using a specified acid as the optically active acid. Claim 8 is for the process of Claim 6 or Claim 7 with the performance of re-crystallisations from acetone. Claim 9 is for the process of Claim 6, Claim 7 or Claim 8 with the formation of a salt in acetone.

16 Claim 10 is for a pharmaceutical composition in which the active ingredient is one or other of the compounds described in Claim 1 to Claim 5 inclusive, together with a pharmaceutically acceptable carrier. Claim 11 is for the pharmaceutical composition of Claim 10 with a specific unit dose of from 0.001 g to 0.100 g of the active ingredient.

THE EARLIER PATENTS

17 The specification of the Patent refers to French Patent No. 2530247 (**the French 4099 Patent**) as having described PCR 4099. The Australian 4099 Patent claims priority from the French 4099 Patent. They are in substantially identical terms. Canadian Patent No. 1194875 (**the Canadian 4099 Patent**) also claims priority from the French 4099 Patent. Sanofi is the registered proprietor of each of the Australian 4099 Patent, the French 4099 Patent and the Canadian 4099 Patent (together the **Earlier Patents**).

18 Apotex and Spirit rely on the ground that the Patent is not novel having regard to the disclosure in the Australian 4099 Patent, the French 4099 Patent and the Canadian 4099 Patent. The Australian 4099 Patent was open to public inspection in Australia on 19 January 1984. The French 4099 Patent was open to public inspection in Australia on 15 March 1984 and the Canadian 4099 Patent was open to public inspection in Australia on 7 November 1985.

THE VALIDITY OF THE CLAIMS

19 It is convenient to deal with the claims in four groups as follows:

- Claim 1.
- Claims 2 to 5.
- Claims 6 to 9.
- Claims 10 and 11.

Claim 1

20 I agree with the conclusion reached by Bennett and Middleton JJ, for the reasons given by their Honours, that there was a disclosure, in the Earlier Patents of the enantiomers of PCR 4099, including the d-enantiomer of the Patent. The enantiomers were expressly claimed. The Earlier Patents disclosed the enantiomers as part of the invention and as compounds predicted to have the relevant beneficial qualities. The relevant skilled addressee of the Earlier Patents would understand to separate the enantiomers and would know the methods to apply. The preparation of the enantiomers was routine and involved no inventive step. Claim 1, in so far as it claims the d-enantiomer, is invalid.

21 Claim 1 extends also to the pharmaceutically acceptable salts of the d-enantiomer. I shall deal with that aspect of Claim 1 when dealing with Claims 2 to 5.

Pharmaceutically Acceptable Salts of Claim 1 and Claims 2 to 5

22 In addition to claiming the d-enantiomer, Claim 1 is also for pharmaceutically acceptable salts of the d-enantiomer. Further, each of Claims 2 to 5 is for a particular salt of the d-enantiomer. Claim 2 narrows Claim 1 by limitation to the hydrochloride salt. Claim 3 narrows Claim 1 by limitation to the hydrogen sulphate, or bisulphate, salt. Claim 4 narrows Claim 1 by limitation to the hydrobromide salt. Claim 5

narrows Claim 1 by limitation to the taurocholate salt.

23 The primary judge found that it was known at the priority date of the Patent that a pharmaceutically acceptable salt was useful for administration of an active compound. Further, the acids chosen in Claims 2 to 5 were conventional and standard methods for their preparation were known at the priority date.

24 The Earlier Patents refer to salts of the compounds disclosed with pharmaceutically acceptable mineral or organics salts. For example, the Canadian 4099 Patent states that the invention also includes:

> the addition salts with pharmaceutically acceptable mineral or organic acids.

Claim 1 of the Canadian 4099 Patent employed the same language. Further, in three different places, Claim 1 of the Canadian 4099 Patent says:

> then the derivative sought is obtained, which is isolated and, if desired, **its** enantiomers are separated and/or **it** is salified by mineral or organic acid action.

In addition, Claim 14 of the Canadian 4099 Patent refers to:

> their addition salts with pharmaceutically acceptable mineral or organic acids.

25 Prior to 1987, hydrochloric acid and sulphuric acid were common laboratory acids and were used to make pharmaceutical salts. Thus, the relevantly skilled addressee would understand the statement of the invention in the Earlier Patents as including a disclosure of addition salts of the compounds, and their enantiomers, with hydrochloric and sulphuric acid.

26 The Canadian 4099 Patent clearly discloses that the invention includes the addition salts with pharmaceutically acceptable mineral or organic acids. It claimed for a process for the preparation of derivatives of the general formula described, and the addition salts of those derivatives with pharmaceutically acceptable mineral or organic acids, whereby a derivative is made and isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid. The reference to **it** being salified is, as a matter of syntax, a reference to the salifaction of the relevant derivative.

27 The Canadian 4099 Patent proffers non-limiting examples to illustrate the invention claimed in that patent. Examples 1, 2, 3 and 13 involve hydrochloride, examples 4, 7, 8 and 9 involve bisulphate and example 10 involves hydrobromide. Thus, the examples disclose addition salts of compounds covered by the general formula disclosed, together with well known mineral acids such as HCl, H_2SO_4 and HBr. There is a clear disclosure of PRC 4099 and its enantiomers, including the d-enantiomer. The skilled addressee would know that that would

include salts with the well known acids HCl, H_2SO_4 and HBr, which are expressly exemplified in the body of the specification.

28 In the light of the earlier Patents, there are quite cogent reasons for concluding that the claim in Claim 1 for pharmaceutically acceptable salts and the claims in Claims 2 to 4 for particular salts of the d-enantiomer are not novel. Thus, the Canadian 4099 Patent effectively directs the skilled addressee to make the hydrochloric, sulphuric and hydrobromic salts of the derivatives of the general formula. One of those derivatives is PCR 4099. The addressee is invited to separate the enantiomers. The reference to salification of the derivatives is an effective disclosure of the salts of the enantiomers made with those acids. That does not require the exercise of any inventive ingenuity or the taking of any inventive step (see *Nicaro Holdings Pty Limited v Martin Engineering Co* (1990) 91 ALR 513 at 531). However, having regard to the conclusion I have reached in relation to lack of inventive step, it is not necessary to form a firm view on the question of novelty in relation to salts of the d-enantiomer.

29 I agree with Bennett and Middleton JJ, for the reasons given by their Honours, that neither the pharmaceutically acceptable salts of the d-enantiomer nor the specific salts of Claims 2 to 5 involved an inventive step, in the light of the common general knowledge as at the priority date of the patent. The common general knowledge included the fundamental principles of stereochemistry, methods for obtaining individual

enantiomers from a racemate and the formation of salts of stereochemical compounds for pharmaceutical purposes.

30 In particular, information concerning diastereomeric salt formation was well known prior to 1987 as a well developed method. Choices were involved, including choices of chiral resolving agent, acid or base as required, and solvent. While trial and error experimentation may have been required, the experimentation was not such as went beyond routine experimentation. The formation of pharmaceutically acceptable salts of both racemates and enantiomers was a common process prior to 1987 and the techniques for that process were known. While a choice was to be made in relation to which salt would be made, a process involving trial and error, and a choice was to be made in terms of acid, both hydrochloric and sulphuric acid were common laboratory acids used to make pharmaceutical salts prior to 1987.

31 The specification of the Patent does not claim an inventive step in the method of obtaining the salts, once the d-enantiomer was known. It was known that a pharmaceutically acceptable salt was useful for administration of an active compound and it was known how to prepare such salts using known mineral or organic acids. Further, the primary judge found that the acids chosen were conventional and that standard methods of preparation were known.

32 The primary judge found that all of the acids used to make the salts of Claims 2 to 5, namely,

hydrochloric acid, sulphuric acid, hydrobromic acid and taurochloric acid, were conventional. Trial and error in the choice of salts involved non-inventive laboratory experiments. Thus, a non-inventive worker in the field, seeking to make a pharmaceutically acceptable salt of the d-enantiomer, on the basis of the unchallenged findings of the primary judge, chose an acid that was readily available and commonly and conventionally used. The non-inventive skilled worker would have been led directly to the salts of Claims 2 to 5 and would apply common processes and techniques to make pharmaceutically acceptable salts of the d-enantiomer including the salts of Claims 2 to 5.

33 It follows that no inventive step was involved in the claim to pharmaceutically salts. Further, no inventive step was involved in the claim for the four specific salts of Claims 2 to 5 inclusive.

Claims 6 to 9

34 Claim 6 is for a process for the preparation of the compound of Claim 1. Claim 7 is based on Claim 6. Claim 8 is dependent upon Claims 6 or 7 and Claim 9 is dependent upon Claims 6, 7 or 8. Thus, Claims 7, 8 and 9 fall with Claim 6.

35 The desire to obtain the compound of Claim 1, the d-enantiomer, is taken for granted. That is to say, the claim is for the means of obtaining the d-enantiomer, not for the decision to do so. The primary judge found that the method used to obtain the compound of Claim 1 was well known in the field in Australia as at the priority date.

Further, his Honour also found that each of the additional integers of Claims 7, 8 and 9 was well known at the priority date and that there were no circumstances to make inventive the choice of the known process described. There was no inventive step in ascertaining the pharmacological characteristics of the enantiomers. The primary judge found that the method of resolution was well known as a means of obtaining enantiomers of a racemic compound as was the chiral resolving agent used.

36 I agree with Bennett and Middleton JJ, for the reasons given by their Honours, that there was no error on the part of the primary judge in concluding that Claims 6 to 9 lacked an inventive step.

Claims 10 and 11

37 Claim 10 is for a pharmaceutical composition comprising, as active ingredient, a compound according to one of Claims 1 to 5, together with a pharmaceutically acceptable carrier. Claim 10 as drafted must fail in so far as it claims a composition comprising as active ingredient the compounds of Claims 1 to 5. The same reasoning applies to Claim 11, which is for a composition according to Claim 10 comprising specified doses of active ingredient.

38 I agree with the conclusion reached by Bennett and Middleton JJ, for the reasons given by their Honours, that there was a disclosure, in

the Earlier Patents, of the active ingredient of that invention with a pharmaceutically acceptable carrier. As indicated above, the Canadian 4099 Patent discloses the d-enantiomer of PCR 4099, the compound of Claim 1 of the Patent. The unit doses of Claim 11 of the Patent are disclosed in the Canadian 4099 Patent.

39 It follows that Claims 10 and 11 are invalid. That was the conclusion reached by the primary judge.

CONCLUSION

40 It follows that all claims of the Patent are invalid. The Patent should be revoked in its entirety. The parties have asked the Court to defer ruling on the question of costs until the substantive questions have been determined.

I certify that the preceding forty (40) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justice Emmett.

Associate: /s/

Dated: 29 September 2009

IN THE FEDERAL COURT OF AUSTRALIA

NEW SOUTH WALES DISTRICT REGISTRY

GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN: **APOTEX PTY LTD (ACN 096 916 148)**
Appellant/Cross-Respondent

AND: **SANOFI-AVENTIS**
First Respondent/ Cross-Appellant

SANOFI-AVENTIS US LLC
Second Respondent/ Cross-Appellant

BRISTOL-MYERS SQUIBB INVESTCO LLC
Third Respondent/ Cross-Appellant

IN THE FEDERAL COURT OF AUSTRALIA

NEW SOUTH WALES DISTRICT REGISTRY

GENERAL DIVISION **NSD 1408 of 2008**

BETWEEN: **SANOFI-AVENTIS**
First Appellant

SANOFI-AVENTIS US LLC
Second Appellant

	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**
JUDGES:	**EMMETT, BENNETT AND MIDDLETON JJ**
DATE:	**29 SEPTEMBER 2009**
PLACE:	**SYDNEY**

REASONS FOR JUDGMENT

BENNETT AND MIDDLETON JJ

41 Apotex Pty Ltd ('Apotex') and Spirit Pharmaceuticals Pty Ltd ('Spirit') seek revocation of Australian Patent No 597784 ('the Patent') pursuant to s 138(3) of the *Patents Act 1990* (Cth) ('the 1990 Act'). Broadly speaking, the Patent claims an enantiomer of a racemate, a process for its preparation and the pharmaceutical compositions containing it. The racemate, designated PCR 4099, was disclosed and claimed in earlier patents filed by the same patentee, Sanofi-Aventis ('Sanofi'), and by its related companies.

42 The grounds relied upon for revocation that are pressed in the appeal are:

- Lack of novelty;
- Lack of inventive step; and
- Not a manner of manufacture.

THE CHEMICAL BACKGROUND

43 The primary judge, at [4] to [11], set out a detailed chemical background which is not in dispute. The relevant matters to note are:

- A racemate, or racemic mixture, consists of two enantiomers, the (+) (dextro) or d-enantiomer and the (-) (levo) or l-enantiomer, in the proportion of 50-50. A racemic mixture consists, statistically, of equal proportions of the two enantiomers.

- A racemate and its enantiomers have the same chemical formula but the enantiomers differ in their structure such that the arrangement of their atoms in space is as non-superimposable mirror images. It is the three-dimensional structure that distinguishes one enantiomer from the other.

- Enantiomers have identical physical and chemical properties except in two important respects:

    1. Enantiomers are optically active and the designation of an enantiomer as (+) (dextro) (d) or (-) (levo) (l) depends on the way in which it rotates polarised light. Enantiomers rotate the plane of polarised light in opposite directions, although in equal amounts.

    2. Enantiomers interact in different ways with other optically active compounds, including reacting with them at different rates. This can result in the enantiomers having different physiological effects, as

to efficacy and toxicity. The relevant physiological activity in this case is inhibition of blood-platelet aggregation.

- It is not possible to designate an enantiomer as (+) or (-) or to determine its properties until the enantiomer is obtained, the plane of polarised light is shone through a sample of the compound dissolved in an appropriate solvent and the extent of the rotation is measured.
- The separation of a racemic mixture, designated (±), into its two optically active enantiomers is called resolution. One process of resolution is diastereomeric salt formation.
- An enantiomer may undergo racemisation (convert to a 1:1 mixture of both enantiomers) *in vivo*.

The enantiomers of PCR 4099

44 Sanofi commenced work on a class of compounds called thienopyridines in 1972. A number of compounds were discovered and developed which ultimately, in July 1980, led to the synthesis of a racemic compound called PCR 4099. Test results indicated that PCR 4099 was better tolerated and more effective than the previously marketed compound. It was one of 21 compounds of the same general formula that were synthesised by Sanofi from about 1976 until 1980. Patents were obtained in various countries, including Australia, France, the United States of

America ('the US') and Canada, in respect of the compounds of that general formula ('the prior art patents'). The Australian prior art patent, with a priority date of 13 July 1982, identified PCR 4099 as example 1 or derivative No 1. The French, Australian and US prior art patents had the same language and description; the Canadian prior art patent was somewhat different.

45 Between 1983 and 1985, development and testing of PCR 4099 resulted in reports of side effects in some animals. In or about November 1985 Sanofi decided to attempt to obtain the enantiomers of that compound. After a number of unsuccessful attempts, Mr Badorc of Sanofi obtained, first, the l-enantiomer of PCR 4099 by diastereomeric salt formation and then the d-enantiomer.

46 Testing of the two enantiomers indicated that the d-enantiomer had all the activity. That is, the d-enantiomer exhibited the same biological activity as the racemic mixture with half the dose. The l-enantiomer had no activity and, further, was less well-tolerated. Indeed, it proved to be more than twice as toxic as the active d-enantiomer.

47 There is no need to recite the chemical background to the claimed invention. It is sufficient to restate a number of propositions that were not in dispute:

- The skilled reader would, as at the priority date, have understood that the compounds of the prior art patents, the new thienopyridines, exist as racemates; that is,

that the chemical structure of these compounds is such that the compounds are optically active.

- The skilled reader would know, on looking at the chemical structure of PCR 4099, that it exists as a racemic mixture.
- Each of the racemate, the (+)-enantiomer and the (-)-enantiomer are properly described by that chemical structure.
- The techniques for resolving a racemate into the two enantiomers were, at the priority date, well-known.

THE PATENT

48 The Patent states that the invention "relates" to a series of products and processes. First, the invention relates to the d-enantiomer of PCR 4099.

49 Second, the invention relates to a process for the preparation of the d-enantiomer.

50 Third, the invention relates to pharmaceutical compositions containing the d-enantiomer.

51 Fourth, the invention relates to the addition salts of the d-enantiomer with pharmaceutically acceptable mineral or organic acids.

52 The specification acknowledges (at page 1(a)) that the formula provided for PCR 4099 represents both the d- and the l-enantiomer as well as the racemic mixture. The specification

acknowledges that the racemic mixture corresponding to the formula was described in the French prior art patent.

53 The specification states that, '[i]*n an unexpected manner*', only the d-enantiomer exhibits the desired activity of inhibition of platelet aggregation, the l-enantiomer being inactive. Further, it is the inactive l-enantiomer that is the less well-tolerated of the two enantiomers. The specification asserts that the preparation and purification of certain salts of the d-enantiomer has proved difficult. As a result of the asserted difficulty in the preparation and purification of the salts of the d-enantiomer, the present invention is also said to relate particularly to specified salts, being mineral and organic acid salts which, it is said, are prepared in a standard manner by the action of the corresponding acid on the base in solution in a solvent from which they precipitate spontaneously or after the addition of a non-solvent of the salt.

The claims of the Patent

54 We shall refer to the enantiomer the subject of the Patent, the dextro-rotatory enantiomer of PCR 4099, as the d-enantiomer, and the other enantiomer, the levo-rotatory enantiomer, as the l-enantiomer.

55 The claims of the Patent are to:

1. The d-enantiomer and its pharmaceutically acceptable salts.

2. The hydrochloride of the d-enantiomer.

3. The hydrogen sulphate of the d-enantiomer.

4. The hydrobromide of the d-enantiomer.

5. The taurocholate of the d-enantiomer.

6. A process for the preparation of the compound according to claim 1, comprising the formation of a salt of PCR 4099 with an optically active acid in a solvent. Repeated recrystallisations of the salt are carried out until a product of constant optical rotatory power is obtained, then the d-enantiomer is liberated from its salt by a base and, if necessary, salt formation is carried out with a pharmaceutically acceptable acid.

7. The process according to claim 6, comprising levo-rotatory camphor-10-sulphonic acid as the optically active acid.

8. The process according to one of claims 6 or 7, comprising the performance of recrystallisations from acetone.

9. The process according to one of claims 6 to 8, comprising the formation of a salt in acetone.

10. A pharmaceutical composition comprising as active ingredient one compound according to one of claims 1 to 5 together with a pharmaceutically acceptable carrier.

11. A composition according to claim 10, comprising unit doses containing from 0.001g to 0.100g of active ingredient.

The primary judge's conclusions as to the claims

56 The primary judge held that:

- Claim 1 was invalid on the ground of lack of novelty;
- Claims 10 and 11 fell with claim 1 and were, therefore, also invalid on the ground of lack of novelty;
- Claims 6 to 9 were invalid on the ground of lack of inventive step; and
- If claim 1 were novel, then it was obvious and did not involve an inventive step.

57 His Honour dismissed all other grounds of invalidity. In particular, his Honour held that claims 2 to 5 were novel and did involve an inventive step and that the invention did involve a manner of manufacture.

THE APPEAL

Sanofi's appeal

58 Sanofi appeals from the primary judge's findings that claims 1, 10 and 11 were invalid for lack of novelty and that claims 1, 6 to 9 and 10 and 11 were invalid for lack of inventive step.

Apotex's appeal

59 In essence, Apotex appeals from the primary judge's finding that claims 2 to 5 of the Patent, which claim specific salts of the d-enantiomer,

were valid. Apotex submits that the primary judge should have found that claims 2 to 5 were invalid on the grounds of lack of novelty, lack of inventive step and no manner of manufacture.

60 In addition, Apotex contends that the primary judge erred:

- In failing to hold that the pharmaceutical compositions of claims 10 and 11 did not involve an inventive step; and
- In holding that claims 1, 10 and 11 involved a manner of manufacture.

Spirit's amended notice of contention

61 Spirit submits that the primary judge was correct in holding that claims 1, 6 to 9 and 10 and 11 were invalid.

62 Spirit contends that the primary judge's decision on the question of novelty should be upheld on a number of additional bases:

1. If it is a requirement under Australian law that there be "enabling disclosure", the prior art satisfies such a requirement.
2. The principles relating to selection patents as explained in *Re IG Farbenindustrie AG's Patents* (1930) 47 RPC 289 are irrelevant to the question of anticipation.
3. If selection patents are relevant to anticipation, a valid selection patent ought not to be made from a small class as in the present case.

4. Claim 1 of the Patent ought to be found to be invalid for want of novelty because of the disclosure in the prior art patents of not only the d-enantiomer of PCR 4099 but also its pharmaceutically acceptable salts.

63 In addition, Spirit contends that the invalidity of claims 1, 10 and 11 should also be upheld on the basis of an absence of manner of manufacture and, to the extent that his Honour did not so find, on the basis of an absence of inventive step in relation to both the d-enantiomer and its pharmaceutically acceptable salts.

64 Spirit also contends that the primary judge erred in failing to hold that claims 10 and 11 did not involve an inventive step when they are dependent on claim 1.

Summary of the issues raised by the appeals

65 In summary, the issues raised by the appeals are:

1. Whether claims 1, 2 to 5 and 10 and 11 are invalid for lack of novelty, lack of inventive step and not being a manner of manufacture; and

2. Whether claims 6 to 9 are invalid for lack of inventive step.

66 The Court, in construing the claims and the prior art, does so putting itself in the position of the skilled addressee in understanding the words

and expressions used and the disclosures of those documents.

NOVELTY

67 In order to understand the submissions concerning the primary judge's findings on novelty, it is necessary to consider the prior art patents said to anticipate the inventions of the claims of the Patent.

The relevant disclosures in the prior art patents

68 The four prior art patents all relate to the same new class of thienopyridines. In each of the prior art patents, the new thienopyridines of the invention have the same general formula in which "X" and "Y" represent a range of possible atoms or other chemical groups. Broadly speaking, the prior art patents claim compounds of the general formula and certain specific derivatives thereof.

69 The prior art patents differ slightly from one another.

The Australian, French and US prior art patents

70 The Australian prior art patent states that it contains a full description of the invention, including the best method of performing it known to the patentee. It sets out the general formula of the new class of thienopyridines and a process for

the preparation of that class of compounds and describes their therapeutic applications as blood-platelet aggregation inhibitors. The patent explains that the compounds, having an asymmetrical carbon, may exist in the form of two enantiomers and continues: '*The invention relates both to each enantiomer and their mixture*'. A process for the preparation of various derivatives is described, including derivative No 1, PCR 4099. There is no process described for the preparation of the enantiomers. It is stated that pharmacological and toxicological tests demonstrate the properties of the derivatives of the invention in terms of toxicity, tolerance and activity. There are claims to the class of compounds and various of the individual derivatives. These are all racemates.

71 Claim 14 claims a therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing as active ingredient a derivative of the general formula, or an addition salt thereof, '*as well as one of the two enantiomers or their mixture*'.

72 The French and US prior art patents are relevantly in the same terms.

The Canadian prior art patent

73 The Canadian prior art patent states that the thienopyridine compounds of the general formula '*include an asymmetrical carbon which may exist in the form of 2 enantiomers. The invention also concerns each of the enantiomers and their mixture*'.

74 Claim 1 is to a process for the preparation of derivatives of general formula (I) '*as well as the 2 enantiomers or their mixture of these compounds of formula (I)*'. Claim 1 states three times during the description of the process: the '*derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified*'.

75 Claim 8 claims a process according to claim 1 for the preparation of PCR 4099. Apotex says that this "picks up" the enantiomers, although they are not specified in claim 8.

76 Claim 14 is the product claim by reference to the compounds of the general formula '*as well as the 2 enantiomers or their mixture of these compounds of formula (I); each time they are obtained by the process of claim 1*'.

What is described in the prior art patents?

77 There is no doubt that the prior art patents describe and claim the enantiomers. There is no qualification to the product claims or to the process claims. Use of the enantiomers of PCR 4099 would infringe the claims of the prior art patents.

78 There is no description of a process to obtain the enantiomers. If the claims of the prior art patents were valid and the patents were to comply with s 40 of the *Patents Act 1952* (Cth) ('the 1952 Act') and the 1990 Act, the patents seem to assume that the worker of ordinary skill did not need a description of the process of

resolution or separation of the enantiomers of the derivatives of formula (I) (including PCR 4099) in order to obtain those claimed enantiomers.

79 Sanofi points out that no process of resolution of the racemate into the constituent enantiomers, or of preparation of the individual enantiomers of the derivatives, is described and that successful separation of the enantiomers was by no means assured, even if the prior art patents contained a direction to do so. Sanofi also says that, until the enantiomers are prepared, it is not known which is the d-enantiomer and which is the l-enantiomer, nor their levels of activity and toxicity. In short, Sanofi submits that further discovery is needed before the invention claimed in the Patent is obtained.

Claim 1 of the Patent

The findings of the primary judge on the novelty of claim 1

80 The primary judge recognised that claim 1 of the Patent claims a chemical compound with a specific property, namely, the ability to rotate plane polarised light to the right. The d-enantiomer is not expressly identified as such in the French prior art patent, nor was there a suggestion that the enantiomers had been separately obtained or tested. His Honour accepted that the skilled reader of the French prior art patent would understand that the compounds there described, including PCR 4099, were racemates and that was "spelled out" in the French prior art patent. However, there was express reference in

the French prior art patent to the enantiomers in terms such as:

- "The invention relates both to each enantiomer and their mixture";
- (In claim 1) "as well as the two enantiomers or their mixture";
- (In claim 14) "as well as one of the two enantiomers or their mixture".

81 Claim 1 of the Canadian prior art patent was to a process for the preparation of derivatives of the general formula:

- "as well as the 2 enantiomers or their mixture";
- "if desired, [the derivative's] enantiomers are separated".

82 Claim 8 of the Canadian prior art patent was to a process for the preparation of PCR 4099:

- "as well as the 2 enantiomers or their mixture" (by incorporation of claim 1).

83 Claim 14 of the Canadian prior art patent was to derivatives of the general formula:

- "as well as the 2 enantiomers or their mixture".

84 The primary judge concluded that the French and corresponding prior art patents each plainly carried the claim that the enantiomers were within the compounds disclosed.

85 A number of matters are not in dispute and were accepted by the primary judge:

- The d-enantiomer is not expressly identified as such in the French prior art patent (or the other prior art patents). While the formula for the racemate and the enantiomers is the same, the stereochemistry was not defined in the prior art patents. Until the enantiomers are obtained, it cannot be predicted which enantiomer rotates plane-polarised light to the left (the l-enantiomer) and which to the right (the d-enantiomer).

- There was and is a range of potential difference in activity between enantiomers. It is not unusual for one enantiomer to display most of the activity and the other little. The activity and toxicity of the enantiomers could not be predicted with certainty until the enantiomers were separated or synthesised and tested.

- A range of techniques for obtaining enantiomers from a racemate was well-known prior to 1987, including diastereomeric salt formation. That method was straightforward and routine, although it involved choices and trial and error experimentation carrying no guarantee of success.

86 Accepting that the only compounds tested in the prior art patents were racemates, his Honour noted that the racemate and the enantiomers had identical chemical formulae and that the basis for the prior art patents was that all

compounds of the class claimed, whether exemplified or not, displayed useful activity. The compounds exemplified differed in their precise effect. No distinction was drawn in the prior art patents between the pharmacological properties of the racemate and the single enantiomers. His Honour concluded that the references to the enantiomers in the prior art patents were consistent only with a disclosure of and a claim to each enantiomer, separate from the racemate and from each other. The prior art patents claimed all compounds within the class disclosed, despite different levels of activity and whether exemplified or not. The prior art patents claimed that a broad class of compounds was effective based on a generalisation from limited results obtained with respect to some of them. That is permissible and not unusual.

87 The primary judge said, at [48], that the claims for the separate enantiomers could be described as "bare claims" for efficacy and that there was no basis for knowing what, if any, efficacy or toxicity would apply to either enantiomer of any particular racemate. His Honour concluded that the d-enantiomer was identified as a compound with useful properties concerning platelet aggregation.

88 His Honour rejected the evidence of those witnesses who denied that the claims of the prior art patents encompassed each of the separated single enantiomers as: '*to say the least, not impressive*'. The primary judge was clearly aware of the need to look at the disclosure of each of the prior art patents and the quality of that

disclosure to the skilled reader. He concluded at [63] that the invention disclosed and claimed by the French prior art patent necessarily carried the implication of a direction, recommendation or suggestion which, if followed, would result in the claimed invention, the d-enantiomer (*Bristol-Myers Squibb Company v FH Faulding & Co Limited* (2000) 97 FCR 524 at [67] per Black CJ and Lehane J).

89 The invention of the prior art patents was not described by reference to a particular result as to efficacy or toxicity and the claims were not so limited. Neither is claim 1 of the Patent. In any event, his Honour pointed out that the formula of PCR 4099 was expressly disclosed as having the claimed advantage and that the same claim was made in relation to each enantiomer of that derivative, so that the enantiomers were disclosed and claim 1 of the Patent is anticipated.

90 In summary, the primary judge noted that the formula of PCR 4099 is identical to the formula of the d-enantiomer claimed in the Patent. His Honour accepted that the skilled but not inventive reader would have understood that each derivative in the French prior art patent and corresponding prior art patents was a racemate and that the technical explanations as to the means of obtaining the derivatives and the testing of them related only to racemates and not to any individual enantiomer. There were, however, express references to the enantiomers in both the body of the specification and in the claims of each of the prior art patents. Those express references, particularly in the Canadian

prior art patent, led the primary judge to conclude that each of the prior art patents '*plainly carry the claim that the enantiomers are within the compounds disclosed*', separate from the racemate and from each other. The fact that the efficacy or toxicity of the enantiomers could not have been known prior to obtaining the enantiomers was not to the point and did not affect that disclosure. His Honour concluded that the invention disclosed and claimed by the French prior art patent '*necessarily carried the implication of a direction, recommendation or suggestion*' to obtain PCR 4099 and its individual enantiomers. His Honour noted that the invention of the French and corresponding prior art patents was not described by reference to a particular result as to efficacy or toxicity and the claims were not so limited. The formula of the racemate was expressly disclosed as having the claimed advantage and the same claim was made in relation to each enantiomer. His Honour rejected the evidence of the Sanofi witnesses that the claims of the prior art patents did not encompass each of the separated single enantiomers of the derivatives.

91 The primary judge gave detailed consideration to the authorities on the requirement for "an enabling disclosure". His Honour's summary was, in part, set out in *H Lundbeck A/S v Alphapharm Pty Ltd* (2009) 81 IPR 228 at [169]. His Honour did not accept that, for the purposes of anticipation of a product claim, there was a separate requirement that the disclosure be "enabling".

92 The primary judge also considered whether the Patent describing and claiming the d-enantiomer could be categorised as a "selection patent". Despite expressing reservations about the concept of selection patents, his Honour concluded that the Patent did not fulfil the requirements for a selection patent as set out in *IG Farbenindustrie* at 322-323 and as restated, in part, in *Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC* (2008) 77 IPR 449 at [105]. His Honour held that, even if there were a special category of "selection patents", the principles did not apply in this case, where the enantiomers were expressly disclosed and claimed in the prior art patents and in the context of the same relevant activity as the racemate, blood-platelet aggregation inhibition. Accordingly, the advantages of the d-enantiomer are not different in kind from those described and predicted in the prior art patents and the claimed activity is not '*out of the range of results predictable from the tests done on the examples in the earlier specification*'.

93 The primary judge found that:

- Claims 1, 10 and 11 are not novel over the prior art patents.
- Claims 1, 10 and 11 cannot be defended from anticipation as valid selections.
- There is no disclosure of the precise formula of claim 3 in the prior art patents. There is not a clear description of the salt of claim 3. There are no clear instructions to do or make that particular salt. The attack on novelty in

relation to claim 3 fails. The same reasoning would apply to claims 2, 4 and 5.

94 His Honour did not deal with the inclusion within claim 1 of the pharmaceutically acceptable salts of the d-enantiomer.

Sanofi's submissions on the novelty of claim 1

95 Sanofi submits that the primary judge incorrectly applied the law. Sanofi submits that the principles stated in *Hill v Evans* (1862) 1A IPR 1 apply to claims to a process and also to claims to a product. It is clear from the authorities, Sanofi says, that to anticipate a claimed invention, a prior paper disclosure that does not itself clearly show the production of the claimed invention must inevitably result in the skilled addressee arriving at the claimed invention.

96 Sanofi submits that the requirement is for clear disclosure and that, in relation to the prior art patents, where:

a. the patentee had not made the d-enantiomer of PCR 4099; and

b. the patentee did not show a method of producing it by resolving it;

c. but it is possible that the skilled addressee, using known methods, might be able to make it;

there is no clear disclosure of the d-enantiomer in the prior art patents.

97 Further, if a requirement for a novelty-defeating prior publication is enablement, those same matters, Sanofi says, show that there was no such enablement.

98 There can be no dispute that each of the prior art patents not only disclosed the racemate but also specifically referred to and claimed the individual enantiomers. Sanofi says that the primary judge erred in his approach which did not, it submits, adequately address what the skilled addressee would understand to have been disclosed in the prior art patents.

99 Sanofi's submission is that, in the context of a product claim, a prior publication is not novelty defeating unless the skilled addressee would have made the claimed invention from the prior disclosure. Sanofi relies for this conclusion on *Hill v Evans* and subsequent authorities and the notion that, to anticipate, the prior disclosure must inevitably result in the skilled addressee arriving at the claimed invention. However, *Hill v Evans* was, in that context, discussing the prior description of a process or method.

100 The relevant question is whether any of the prior art patents describe the claimed invention with sufficient clarity to the skilled reader (*Bristol-Myers Squibb* at [67]).

101 Sanofi submits that, had a claim been made in the prior art patents for the efficacy of the enantiomers separately, the claim would properly be described as a "bare claim" without any support in the specification. It says that the addressee of the Canadian prior art patent (and

the other prior art patents) would know that one cannot know which of the enantiomers has the desired activity without making and testing them. It says that further discovery was needed before it was known that the d-enantiomer should be chosen and '*before the claimed invention* [was] *obtained*'. Further, apparently ignoring the direction to obtain the enantiomers "if desired", it says that there are no clear or unmistakable directions to make the d-enantiomer and that, even if there were, no one had previously separated the enantiomers of PCR 4099. Although diastereomeric salt formation and asymmetric synthesis were routine methods applied to obtaining enantiomers from a racemate, Sanofi says that those methods were not assured to work on PCR 4099.

102 It is worth noting that the primary judge did not accept the evidence of Sanofi's witness, Mr Badorc, as to the difficulties encountered in the separation process of diastereomeric salt formation. In that regard, his Honour's findings differed from those in some other courts, for example in Canada and the US. The primary judge concluded that the work of Mr Badorc did not involve any inventive step and that the steps that he took were typical of the trial and error that was necessarily involved with the use of the technique of diastereomeric salt formation.

Consideration of the novelty of claim 1

103 It is to be recalled that the invention claimed in claim 1 of the Patent is to a product alone: the

d-enantiomer of PCR 4099 and to its pharmaceutically acceptable salts, unlimited as to use or purpose, or level of activity or toxicity, or as a product of a process. The question whether a prior publication anticipates a subsequent claimed invention depends upon the quality of the disclosure in that prior publication, as assessed through the eyes of the skilled addressee. Apotex accepts that a disclosure will not be sufficiently clear if it is necessary to supplement the disclosure by means of experiments or other sources of information in order to perceive the disclosure. However, that is not the same as accepting that, where there has been disclosure of a product, the method of producing that product must also be disclosed.

104 Some of the same issues concerning novelty arose in *Lundbeck*, a case which also involved a claim to the (+)-enantiomer of a racemate. From the consideration in *Lundbeck*, the following is apposite to the consideration of anticipation by the prior art patents in this case:

- Where the prior publication discloses exactly what is claimed, there is anticipation (*Lundbeck* at [180]).

- There is anticipation if the skilled addressee would add missing information to what is disclosed in the prior art as a matter of course and without the application of inventive ingenuity or undue experimentation (at [181]). A disclosure is sufficient if it enables the skilled addressee, in the ordinary course and without invention, to add what is

missing in the prior publication to obtain the claimed invention (at [183]).

- If the prior art discloses the very subject matter of the invention, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work (at [189]). If the disclosure is of an invention which, if performed, would infringe the patent, there is anticipation.

- The question is whether the disclosure is sufficient to enable the skilled addressee to perceive, understand and, where appropriate, apply the prior disclosure necessarily, but within the ordinary limits of trial and error, to obtain the invention (at [190]).

105 In *Lundbeck*, there was no reference to the enantiomers in the prior patent for the racemate. The prior patent disclosing and claiming the racemate did not render the claims to an individual enantiomer invalid for lack of novelty. A prior art article, the Smith article, made reference to the R and S enantiomers of the racemate but not to the (+) and (–) (or d and l) enantiomers. There is no correlation between the R and S designations and the (+) and (–) designations. There was no anticipation in circumstances where the reference to the R and S enantiomers and the knowledge that a racemic mixture contains enantiomers were not sufficient to disclose the (+) and (-) enantiomers and where the preparation of the (+)-enantiomer involved an inventive step or undue experimentation.

106 In this case, there was a disclosure of the enantiomers in the prior art patents. Those enantiomers were not only described, they were also claimed. Thus there was a clear direction to the skilled reader to prepare the enantiomers and in addition, but not necessarily, it was made clear that such enantiomers were, or were likely to be, useful for the desired purpose. The primary judge was not in error in concluding that the prior art patents disclosed the enantiomers as part of the invention and as compounds predicted to have the beneficial qualities of the compounds exemplified. If his Honour were correct in his conclusion that the skilled reader would understand to separate the enantiomers and would know the methods to apply, and that the preparation of the d-enantiomer was routine and involved no inventive step, it is hard to see how his Honour erred in concluding that there had been disclosure of the d-enantiomer to the skilled addressee and that a claim to the d-enantiomer had been anticipated (*Ranbaxy*).

107 Sanofi emphasises that it was not possible without separation and testing of the enantiomers to predict with certainty their activity or toxicity, or which enantiomer should be chosen and which excluded for the purposes of the desired activity. Further, it says, while a range of techniques for obtaining enantiomers from a racemate were well-known prior to the priority date, choices were involved in the well-known method of diastereomeric salt formation and trial and error experimentation carried no guarantee of success.

108 Sanofi's submissions seem to suggest that unless the claimed compound was actually made and the making of it described in the prior publication, there could be no anticipation. We do not accept that submission. Sanofi appears to submit that it would have been necessary for the prior publication to describe, or for the evidence to establish, a prior resolution of PCR 4099 or, at least, of a compound of the general formula as claimed in each of the prior art patents. That is, Sanofi's submissions are to the effect that it would be necessary for a prior publication, in every case, to set out the method of preparation, no matter how routine, and presumably the detailed methodology of each step taken in the preparative process. That cannot be correct.

109 That is not to say that the disclosure of a racemate will, by itself, anticipate a later claim to an enantiomer of that racemate. It may do so or it may not. That will depend on the evidence of the skilled addressee and the particular context.

110 Sanofi draws in aid the fact that each of the prior art patents suggests that PCR 4099 would have the desirable activity and lack of toxicity so that, despite the references to the enantiomers, there was a "teaching away" of the undertaking of the preparation of the enantiomers. For the reasons in *Lundbeck*, this is not an answer to the claim of lack of novelty. In any event, there was a teaching that the racemate was useful but there was also a teaching that the individual enantiomers would be expected to display activity.

Selection patents

111 The primary judge expressed some doubt about the applicability in Australia of the concept of selection patents but proceeded to consider the criteria for such a patent as set out in *IG Farbenindustrie* and as referred to by the Full Court in *Ranbaxy* in the context of a consideration of false suggestion. In *Ranbaxy*, IP Australia considered the patentee's submissions to be that the claimed invention could be considered a selection.

112 His Honour said at [79] that, in his view and after considering various authorities, the concept does not recognise a special class of patents but '*is a convenient shorthand to pick up the relevant principles concerning anticipation*'.

113 As summarised by the Full Court in *Ranbaxy* at [105], in order to advance the proposition that the claimed invention constitutes a "selection" such that it is not anticipated by the disclosure of a class of compounds of which it is a member, the claimed member has to satisfy certain requirements:

- There must be some substantial advantage to be secured by the use of the selected members;
- The whole of the selected members must possess the advantage in question;
- The selection must be in respect of a quality of a special character, which can fairly be said to be peculiar to the group; and

- The advantage possessed by the selected members must be clearly disclosed in the specification.

114 The primary judge found that, if a selection were available, it could be satisfied by the selection of the d-enantiomer from the class comprising the d-enantiomer, the l-enantiomer and the racemate. His Honour concluded that there is a substantial advantage to be secured by the use of the d-enantiomer as compared with the use of either the racemic mixture or the l-enantiomer. That advantage is that the d-enantiomer is better tolerated or less toxic and as effective as the racemate at a lesser concentration. Clearly, as his Honour said, the second and fourth criteria are also satisfied.

115 However, the primary judge concluded that the third criterion was not satisfied, as the French and corresponding prior art patents described the advantages very generally, the claims were not limited to any particular result and it was not claimed that each compound within the class described would have equal qualities. That is, the qualities of the d-enantiomer were not of a special character in exerting an effect on blood-platelet aggregation, Rather, the differences exhibited in activity and toxicity were quantitative differences. Such quantitative differences were envisaged in the prior art patents. His Honour said that the results for the d-enantiomer were by no means out of the range of results predictable from the tests done on the examples in the earlier specifications. His Honour also found, and it is not challenged, that it was part of the

common general knowledge that there was a range of potential difference in activity between enantiomers and that one enantiomer may have all of the activity and the other none. Further, it was not unusual for one enantiomer to display most of the activity and the other little (at [35(4)(ii)]). That is, the advantages of the characteristics of the d-enantiomer were not unexpected (at [86]-[87]). No other special advantages are described in the Patent.

116 Sanofi supports the primary judge's characterisation at [81] of the class from which the selection was made as the racemate, the selected enantiomer and the non-selected enantiomer. Sanofi observes that his Honour equated the requirement of a "quality of a special character" with "unexpectedness" and submits that the characteristics of the d-enantiomer were unexpected. It says that the fact that one enantiomer of the class exhibits all of the activity and the other none, and that the active enantiomer is well-tolerated, could not have been predicted where there is a range of potential difference in activity and toxicity. As such, it submits that the result was unexpected, as were certain additional advantages, such as the fact that the d-enantiomer does not undergo racemisation or interconversion in the body.

117 It is not necessary to decide whether or not there is a special category of "selection patents" which, if they satisfy the test in *IG Farbenindustrie*, may overcome a claim of lack of novelty. Any such category was not, in our view, intended to exclude from the requirement of

novelty a compound (here, the d-enantiomer) that was previously disclosed and claimed as one of a class of inventive compounds that demonstrated, or were predicted to demonstrate, particular activity and tolerance at various levels, and the compound was then shown to demonstrate that same activity at a high level, with high tolerance.

118 Assuming for the purposes of this appeal, without deciding, that there is a category of "selection patents", the d-enantiomer is not novel over the prior art patents.

The pharmaceutically acceptable salts of the d-enantiomer

119 As has been noted, claim 1 of the Patent is to the d-enantiomer of PCR 4099 and its pharmaceutically acceptable salts. Claim 3 is to a specific salt of the d-enantiomer, the hydrogen sulphate salt. Claims 2, 4 and 5 are to other specific salts.

120 Apotex relies on the following reference in the Canadian prior art patent as an anticipation ('the Expression'):

> . . . then the derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action; . . .
>
> (Emphasis added).

121 The primary judge was of the view that the prior art patents most naturally refer to the salts of the racemate rather than of the enantiomers. We agree.

122 His Honour also said that, even if the salification referred to the enantiomers, there was a choice of acid to be made, so that there was not the necessary disclosure to anticipate a claim to a particular salt, either by providing a clear description of the salt (for example, of claim 3) or by providing clear instructions to do or make that particular salt. Sanofi points to the evidence that, while the method of preparation of the salts may be standard, there was a choice to be made in relation to which salt of the d-enantiomer to make. That process, it says, involved trial and error, and a choice in terms of acid, to produce a salt with appropriate properties such as being able to crystallise easily, not being hygroscopic and being sufficiently water-soluble. Consequently, the skilled reader could not predict that a particular acid would result in a pharmaceutically acceptable salt of the d-enantiomer.

Claim 1 and the pharmaceutically acceptable salts of the d-enantiomer

123 Claim I of the patent is not only to the d-enantiomer of PCR 4099 but also to its pharmaceutically acceptable salts. The primary judge did not consider the latter part of claim 1. The claim to the d-enantiomer is not novel, being anticipated by the prior art patents.

124 Using the Canadian prior art patent to examine what is said in the prior art patents concerning the pharmaceutical salts of the compounds of the invention:

- The specification states:

  > These compounds include an asymmetrical carbon which may exist in the form of 2 enantiomers. The invention also concerns each of the enantiomers and their mixture.
  >
  > The invention also includes the addition salts with pharmaceutically acceptable mineral or organic acids . . .

- The examples are of salts of the racemic mixtures, for example, hydrochloride and bisulphate (ie. hydrogen sulphate) salts.

- All of the pharmacological and toxicological results presented for the salts are for salts of racemates.

- Claim 1 is to a process for the preparation of derivatives of the given general formula (formula (I)) and their addition salts with pharmaceutically acceptable mineral or organic acids or with mineral bases, as well as the two enantiomers or their mixture of the compounds of formula (I). The claim does not link the enantiomers to the addition salts.

- Claim 1 then continues with the Expression. The Expression (or an expression relevantly the same) appears three times in the claim. The Expression does not link the enantiomers to the addition salts.

- Claim 14 refers to the enantiomers but that reference does not link the enantiomers to addition salts: '*Derivatives of general formula*

> *(I) . . . and their addition salts with pharmaceutically acceptable mineral or organic acids . . . or with mineral bases . . . ; as well as the 2 enantiomers or their mixture of these compounds of formula (I)*'.

125 We do not accept Apotex's or Spirit's submission that the references, in context, are to the pharmaceutical salts of the enantiomers.

126 Turning to the Australian prior art patent and bearing in mind that the derivatives of formula (I) were racemates, the specification contains the general statement:

> Thus, the invention also relates to a therapeutic composition having in particular an inhibiting action on blood-platelet aggregation and anti-thrombotic action, wherein the active ingredient is a derivative of the formula (I) or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid . . . or with a mineral base . . .
>
> (Emphasis added).

127 Claim 14 of the Australian prior art patent claims a therapeutic composition containing as active ingredient a derivative of formula (I) as claimed in claim 1, '*or an addition salt* ***thereof*** *with a pharmaceutically acceptable mineral or organic acid or with mineral bases,* ***as well as*** *one of the two enantiomers or their mixture*' (emphasis added).

128 These are not disclosures of the pharmaceutical salts of the enantiomers. The disclosures

of the French and US prior art patents are relevantly in the same terms.

129 It is clearly stated in each of the prior art patents that the invention therein described relates not only to the racemic mixture of the two enantiomers but also to each enantiomer of, *inter alia*, PCR 4099. For example, the Australian prior art patent states that '[t]*he invention relates both to each enantiomer and their mixture*'. However, the disclosures of addition salts and pharmaceutically acceptable salts are of the racemates. That reading of the prior art patents is consistent with evidence from skilled addressees. The pharmacological and toxicological tests were also of the salts of the racemate.

130 The specification of the Patent states that the invention which relates to the d-enantiomer of PCR 4099 relates also to the addition salts of the d-enantiomer with pharmaceutically acceptable mineral or organic acids. The Patent also makes reference to the difficulty of purifying the d-enantiomer, which is an oil, and states that it is preferable to use crystalline products which can usually be purified by recrystallisation. Sanofi concedes that there was nothing inventive in the method of salt formation in the Patent and that it was generally the same technique as described in the Canadian prior art patent. However, the specification says that the purification of at least some salts proved to be difficult and that some had undesirable properties (such as being hygroscopic). While the salts are prepared '*in a standard manner by the action of the corresponding acid on the base in solution in a solvent*', it

required finding salts which crystallise easily, are not hygroscopic and are sufficiently water-soluble.

131 The pharmaceutically acceptable salts of the d-enantiomer were not anticipated and are novel over the prior art patents.

Conclusion on the novelty of claim 1 of the Patent

132 The enantiomers of PCR 4099 were disclosed and claimed in each of the prior art patents. Further, the prior art patents each contained a direction, recommendation or suggestion which, if followed, would result in the d-enantiomer of PCR 4099. A range of techniques for obtaining enantiomers from a racemate was known and commonly applied prior to 1987. If his Honour were correct in his conclusion that the process used to obtain the enantiomers of PCR 4099 was obvious then, in our view, this further constituted each of the prior art patents as a novelty-defeating disclosure of the d-enantiomer. However, the pharmaceutically acceptable salts of the d-enantiomer were not disclosed in any of the prior art patents. The only salts disclosed were those of the racemate. Accordingly, the pharmaceutically acceptable salts of the d-enantiomer were not anticipated and are novel over the prior art patents.

Claims 2 to 5 of the Patent

The findings of the primary judge on the novelty of claims 2 to 5

133 The primary judge found that the invention as claimed in each of claims 2 to 5 was not anticipated, not having been disclosed in the prior art patents, on the basis that:

- There was no disclosure of the precise formula of claims 2 to 5;
- The specifications of the prior art patents most naturally refer to salts of the racemate rather than of the enantiomers;
- There is a choice of acid to be made in relation to making salts of the d-enantiomer;
- There was not a clear description of the salts described in claims 2 to 5; and
- There were no clear instructions to make the particular salts of claims 2 to 5.

134 The prior art patents refer to and therefore direct the reader to mineral acids and organic acids. The three salts of claims 2 to 4 of the Patent, hydrochloride, hydrogen sulphate and hydrobromide, are all mineral salts. The salt of claim 6, taurocholate, is an organic salt. However, while there were examples of similar salts of the racemates provided, this was not sufficient to constitute a direction that would inevitably lead to the subject matter of claims 2 to 5, particularly in circumstances where many other salts could have been chosen and used.

Apotex's and Spirit's submissions on the novelty of claims 2 to 5

135 Apotex and Spirit submit that the prior art patents disclose the enantiomers and the addition salts of the enantiomers with pharmaceutically acceptable mineral or organic acids. To the extent that this submission is based on the Expression and on claims 1 and 14 of the Canadian prior art patent, the salts of the enantiomers are not thereby disclosed. Apotex then submits that, even if the salts as described and exemplified in the prior art patents are of the racemates, including PCR 4099, and not of the enantiomers, the examples are said to be non-limiting and that the mineral acids used in the examples are commonly used pharmaceutically acceptable mineral acids, Although the only express combination of PCR 4099 is with hydrochloric acid in the prior art patents, Apotex submits that all that is required of the skilled addressee '*is merely to realise that the addition salts disclosed include PCR 4099 . . . and its enantiomers, with another common mineral acid, sulfuric acid*', which does not, Apotex says, require inventive ingenuity or an inventive step. The same would apply to the combination of PCR 4099 and its enantiomers with hydrobromic and taurocholic acids. The latter acid is not referred to in any of the prior art patents.

Consideration of the novelty of claims 2 to 5

136 There is no direction in the prior art patents, let alone a direction that would inevitably or without undue experimentation lead to the

claimed invention of claims 2 to 5. The skilled reader would be required to take from the prior art patents the disclosure that he or she should make the pharmaceutically acceptable salts of the d-enantiomer of PCR 4099, to know the method to apply to make a salt of the d-enantiomer of that derivative and to choose the specific salts out of the possible range of mineral and organic acids. A hydrogen sulphate salt and a hydrobromide salt of derivatives other than PCR 4099 are disclosed in the prior art patents. However, in the case of claims 3 and 4 of the Patent, the skilled reader would have to know to choose a salt not exemplified in the prior art patents for PCR 4099. No salt using taurocholic acid is exemplified in the prior art patents. This is not a case where, as Apotex submits, the skilled reader has "merely" to follow the "teaching" of the prior art patents. There is no instruction or direction or teaching in any of those patents in relation to the salts of the d-enantiomer as claimed in claims 2 to 5.

137 The requirement for lack of novelty is that the prior publication anticipate or disclose the claimed invention, not that it renders it obvious to the skilled reader to apply or try to apply what is disclosed for one compound to another. It is not a case where the examples demonstrate that a technique is applicable to some members of a class of compounds, being enantiomers of the derivatives of formula (I), and can then be said to be disclosed as applicable to the whole of the class. The prior art patents do not say to make, nor do they exemplify, the salts of the enantiomers. The direction is limited to the racemic

mixtures. There is no clear description of, or clear instructions to make, something that would infringe the subsequent claims to the salts of the enantiomers. Even if there were a direction to make a salt of the enantiomers, the direction could be carried out in a way that would not result in infringement of claims 2, 3, 4 or 5 and that does not constitute anticipation (*General Tire & Rubber Company v Firestone Tyre and Rubber Company Ltd* (1971) 1A IPR 121; *Olin Corporation v Super Cartridge Co Pty Ltd* (1977) 180 CLR 236; *Lundbeck* at [169] and [173]).

138 As the primary judge said at [89], there is not, in any of the prior art patents, a clear description of the salts described in claim 3 (or claims 2 or 4 or 5) or clear instructions to do or make that particular salt. The prior art patents do specify three of the specific salts as salts of a racemate. That is not sufficient to constitute an anticipation of the choice of salt of one of the enantiomers of PCR 4099. There was no direction to salify the d-enantiomer of PCR 4099, let alone to make the particular salts of claims 2 to 5.

139 Apotex says that for the prior art patents to exclude the salts of the enantiomers offends against common sense. We are not satisfied that that is the case. The prior art patents were drafted by the patentee, presumably carefully. The enantiomers were not described as having been obtained but they were disclosed and claimed. The patentee may have had good reason for not describing or claiming the application of a process to a product not yet produced.

140 Apotex has not demonstrated that the primary judge was in error in concluding that claims 2 to 5 were novel.

Claims 10 and 11 of the Patent

141 The primary judge said that his conclusion as to claim 1 "also affects" claims 10 and 11. Those claims are to pharmaceutical compositions comprising as active ingredient one compound of one of the claims 1 to 5.

142 Spirit points to the statement in the Canadian prior art patent, in general terms, that the drug of the invention may be orally administered in the form of tablets, coated tablets, capsules, drops, granules or syrup and in a dose from 0.005g to 0.250g of a derivative of the invention, the daily dosage regimen varying within the range from 0.005g to 1.00g of active ingredient. Examples disclose pharmaceutically acceptable carriers within the description in claim 10 of the Patent and doses within the range of claim 11 of the Patent. The examples of the formulations of five of the derivatives, which comprise the active ingredient with a pharmaceutically acceptable carrier, are stated to be "non-limiting".

143 The Canadian prior art patent discloses, generally, "the drug of the invention", which includes the d-enantiomer of PCR 4099, with pharmaceutically acceptable carriers, thus anticipating claim 10 of the Patent which claims a pharmaceutical composition comprising as active ingredient one compound of one of claims 1 to 5 in that form.

144 Claim 11 of the Patent is to a composition according to claim 10, comprising unit doses containing from 0.001g to 0.100g of active ingredient. The non-limiting examples of the formulation of the Canadian prior art patent contain the active ingredient in a range that intersects with the range claimed in claim 11. The active ingredient of the Canadian prior art patent includes the enantiomers of PCR 4099. This anticipates claim 11 of the Patent.

OBVIOUSNESS

The starting point for the assessment of obviousness

145 It is not in dispute that the obviousness of the claims of the Patent is to be assessed under s 100(1)(e) of the 1952 Act. That is, whether '*the invention so far as claimed in any claim of the complete specification . . . was obvious and did not involve an inventive step having regard to what was known or used in Australia on or before the priority date of that claim*'.

146 In *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* (2007) 235 CLR 173, the High Court restated, shortly, the history of the introduction of obviousness as a ground of invalidity and the distinction between novelty and obviousness. The Court also emphasised the balance of policy considerations in patent law, to encourage and reward inventors without impeding advances and improvements by skilled, non-inventive persons. The High Court reaffirmed at [51]-[56] a number of the principles to

be applied to a determination of obviousness including, relevantly:

- "Obvious" means "very plain".
- The question whether an invention is obvious is a question of fact.
- The question of inventive step is one of degree. Ingenuity is relative, depending on relevant states of common general knowledge.
- The question is always *'is the step taken over the prior art an "obvious step" or "an inventive step"'*.
- There is no distinction between obviousness and a lack of inventive step.
- There must be "some difficulty overcome, some barrier crossed".
- The essential question to be posed when considering obviousness under the 1952 Act was that set out in *Wellcome Foundation Limited v VR Laboratories (Aust) Proprietary Limited* (1981) 148 CLR 262: the question of obviousness involves asking whether **the invention** would have been obvious to a non-inventive worker in the field, equipped with the common general knowledge in that field, without regard to documents in existence but not part of common general knowledge.
- Common general knowledge, as explained in *Minnesota Mining and Manufacturing Company v Beiersdorf (Australia) Limited* (1980)

144 CLR 253 at 292, is the background knowledge and experience which is available to all in the trade in considering the making of new products, or the making of improvements in old.

- For the purpose of determining inventiveness, prior disclosures which were not part of common general knowledge are excluded from consideration.

147 The High Court in *Lockwood (No 2)* also made some general observations regarding the patentability of ideas:

- An invention may, and usually does, involve three processes:
  - The definition of the problem to be solved or the difficulties to be overcome;
  - The choice of the general principle to be applied in solving this problem or overcoming these difficulties; and
  - The choice of the particular means used.

  Merit in any one of these stages, or in the whole combined, may support the invention.
- There is a distinction between the idea or concept or principle informing an invention and the means of carrying it out or embodying it in a manner of new manufacture.
- Invention may lie in the idea of taking the step in question. An inventive step can be having an insight rather than a mere development and application of existing ideas.

148 Apotex claims that all of the claims in dispute are obvious but accepts that this depends on the starting point for that assessment. Apotex contends that the correct starting point is the racemic mixture, PCR 4099. As neither that compound nor any of the prior art patents were part of common general knowledge in Australia at the priority date, Apotex accepts that if common general knowledge is the starting point, the claims are not obvious. Sanofi contends that the correct starting point is the common general knowledge of the hypothetical non-inventive worker in the field as at the priority date of the Patent.

149 There is no dispute that '*what was known or used in Australia*' (s 100(1)(e) of the 1952 Act) means the common general knowledge in the relevant field (*Minnesota Mining*). If PCR 4099 is the correct starting point, Apotex and Spirit rely on the unchallenged findings of the primary judge as to the content of common general knowledge in support of their assertion that the subject matter of the claims was obvious.

150 Apotex submits that the primary judge erred in applying different starting points for the purpose of assessing the obviousness of different claims. In any event, the key issue is the correct starting point.

151 Obviousness and inventive step are antitheses. What is obvious does not involve an inventive step and vice versa (*Lockwood (No 2)* at [52]).

152 Section 100(1)(e) makes it clear that the question to be addressed is whether **the invention**, so far as claimed in the particular claim, is obvious and does not involve an inventive step. That requires a determination of the invention, as described in the specification. What is claimed may then equate with, or be less than the totality of or scope of, the invention. The specification of the Patent makes it clear that the selection of PCR 4099 as the racemate to be resolved formed no part of this invention as described and claimed. From the primary judge's reasons, no such claim was made. It was the process of separation of the enantiomers of that mixture to obtain the enantiomers, and, in turn, the pharmaceutically acceptable salts of the d-enantiomer, that broadly, were the subject matter of the claims. The invention to be assessed for obviousness is ascertained from the patent and the obviousness or inventive step of the invention as claimed is then assessed by reference to common general knowledge in Australia at the priority date.

153 This analysis of the invention assists in determining the correct starting point for the application of the common general knowledge of the hypothetical person of skill in the art in order to decide whether the invention as claimed in the claims was obvious or involved an inventive step. The invention presupposes that the hypothetical worker was in possession of the racemate and the knowledge that it had platelet aggregation inhibiting activity. As the primary judge said, the desire to separate the enantiomers should be taken for granted. Knowledge of the kind of

activity was a prerequisite to testing the enantiomers for that activity which led to the asserted unexpected result that the l-enantiomer did not exhibit any such activity. However, the hypothetical skilled worker would not know the contents of the French prior art patent or, indeed, the other prior art patents, that were not part of common general knowledge.

154 The "problem/solution approach" yields the same result.

155 In *Wellcome*, Aickin J expressed the test for obviousness as:

> whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they be the steps of the inventor or not.

156 *Minnesota Mining* at 292 talks of the '*process of applying such common general knowledge to the solution of a problem*'.

157 In *Aktiebolaget Hässle v Alphapharm Pty Limited* (2002) 212 CLR 411, the patentee accepted that the notional addressee is to be told the nature of the problem but is not provided with information not part of common general knowledge and obtainable only by testing. The majority, Gleeson CJ, Gaudron, Gummow and Hayne JJ, referred at [40] to what was said by Lord Hoffmann in *Biogen Inc v Medeva plc* (1996) 36 IPR 438:

> A proper statement of the inventive concept needs to include some express or implied reference to the problem which it required invention to overcome.

158 While their Honours apparently questioned the English (and European) approach of "problem and solution", they referred to the earlier acknowledgment by Buckley LJ in *Re Beecham Group Ltd's (Amoxycillin) Application* [1980] 97 RPC 261 to the solution of '*some recognised problem*' and the meeting of '*some recognised need*'. Their Honours also referred expressly to the consistory clause in the Hassle patent, which stated that the claimed invention was designed to obtain a pharmaceutical dosage form of omeprazole to answer the problems identified in the specification. Omeprazole itself was not part of common general knowledge. Their Honours stated that it was the interaction between the combination of integers of the formulation that was the essential requirement for the presence of an inventive step.

159 The High Court in *Lockwood (No 2)* re-stated or clarified its position on the "problem and solution" approach and, again, cited the reference of Lord Hoffmann in *Biogen Inc* to the problem which it required invention to overcome. The High Court now makes it apparent that it does not reject such an approach, where appropriate. The question of obviousness is not confined to a problem/solution approach. It may not be appropriate or sufficient where, for example, no skilled person in the art had thought of a general

idea or general method of solving a known difficulty with respect to a known product or where the appreciation that there was a problem with a known product was itself part of the inventive concept. As the High Court said at [105], while not every invention constitutes a solution to a problem, it is commonplace so to describe an invention where it is appropriate to do so. However, admissions about a problem in a specification need to be weighed with evidence of the perception of any problem by the person of skill in the relevant art, before exposure to the solution contained in the invention.

160 The problem addressed in the Patent is the resolution of the enantiomers of PCR 4099. The problem described is the difficulty of purifying the d-enantiomer and of obtaining suitable salts. Accordingly, the hypothetical skilled worker armed with common general knowledge would have that racemic mixture as the starting point. The question is then whether, from that starting point, the claimed invention was obvious; whether there was an inventive step, as assessed by reference to the common general knowledge, in resolving the enantiomers and obtaining pharmaceutically acceptable salts of the d-enantiomer. It should be emphasised that the base line or starting point may itself be part of the inventive step or inventive process but that is not the case here. The selection of PCR 4099 for resolution was not claimed to be inventive.

161 The French prior art patent as referred to in the specification of the Patent does assist in understanding the starting point and context of

the invention described and claimed. However, it is clear, as the primary judge accepted, that the reference to the French prior art patent in the specification of the Patent does not make that patent part of common general knowledge. It does not make that patent available to tell the notional skilled addressee the results of the testing of formulations of PCR 4099.

162 As the Full Court said in *Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20, close attention should be given to the terms of the individual specification to understand what admissions are made and also to understand the invention. In *Insta*, previous patents of the same inventor were cited but this did not constitute an admission that the inventions the subject of those patents had become part of common general knowledge. Rather, the specification described the inventor's own inventive journey (at [84]) and his own familiarity with the inventions the subject of earlier US patents (at [104]). Importantly, the claim in that case was to an entire structure or construction, which included the subject matter of those earlier US patents with additional features described in the specification. The invention was not limited to the introduction of new features into an existing structure (at [92]).

163 Sanofi chose to file a separate patent for the claimed invention, the d-enantiomer, its pharmaceutically acceptable salts and the process for obtaining that enantiomer from the racemic mixture of PCR 4099. The invention of the Patent starts with a biologically active racemate.

Common general knowledge

164 The primary judge made a number of findings concerning common general knowledge as at the priority date of the Patent in relation to:

- The fundamental principles of stereochemistry;
- Methods for obtaining individual enantiomers from a racemate;
- The formation of salts of stereochemical compounds for pharmaceutical purposes; and
- The biological/pharmacological activity and toxicity of stereochemical compounds and the ability to predict same.

165 There is no dispute with his Honour's findings at [35] and [36] as indicative of the state of common general knowledge in the relevant field in Australia as at the priority date of the Patent in relation to each of these four issues, which would also be matters understood by and known to the skilled addresses of the Patent.

166 At [35] of his reasons the primary judge distilled from the evidence of the expert witnesses the state of common general knowledge in the relevant field in Australia by 1987:

> (1) The principles of stereochemistry were well known prior to 1987. They, as well as information concerning techniques for obtaining enantiomers, were taught to undergraduate students, and university students more generally, from the 1960s through to 1987. There have been no

significant changes in the science of stereochemistry since 1987, though certain advances have been made in the understanding and application of certain techniques for obtaining enantiomers, asymmetric synthesis being an example

(2) (i) A range of techniques for obtaining enantiomers from a racemate was well known prior to 1987. Information concerning those techniques, and in particular diastereomeric salt formation, were taught to undergraduate students from the 1960s, though this may not always have involved practical experimentation. Asymmetric synthesis was also a known technique, though query whether it was to be understood as a "separation" technique.

(ii) Prior to 1987, diastereomeric salt formation was a well developed method, which was straightforward and routine, though involving choices. Those choices included choices of chiral resolving agent (acid or base as required) and solvent. The variety of choices in that regard, as well as certain other factors, meant that the process may well involve trial and error experimentation carrying no guarantee of success. That was, however, not such as to take the process beyond routine experimentation, including

in respect of parallel experimentation. Though a choice certainly existed in the drug development process as to whether to obtain enantiomers by diastereomeric salt formation or, say, asymmetric synthesis instead, or indeed simply to undertake a wider structure-activity study in the relevant class of compounds, diastereomeric salt formation was certainly a prominent, widely used and well developed technique prior to 1987. It is clear that many would have elected to use that technique as a first step, though there was obvious disagreement on that point. Though not without certain difficulties, the process had been known and reported to yield results, though not necessarily in relation to thienopyridine compounds.

(iii) As to the resolving acid or base, and solvent, there were clearly choices to be made in this regard. Guidance could be gained from the literature, though principally, it would appear, where similar compounds had already been resolved. Lists of standard chiral acids and amines were also available. Camphor-10-sulfonic acid was known as a chiral resolving agent prior to 1987 and its use was not new. Its commercial availability in both enantiomeric

forms was perhaps not certain, though it was possible to prepare a chiral form of the acid. Acetone was a well known and commonly used solvent prior to 1987. Further variables such as the temperature at which the experiment was conducted, the sealing and shape of the reaction vessel, the concentration of racemate to reagent and solvent respectively, the amount of solvent present and the room temperature, were variables to be dealt with as part of the normal experimentation process. As Apotex alluded to in its submissions, details as to those variables did not appear to warrant particular focus in the patent in suit.

(iv) The time that might be expected to elapse before obtaining a yield from the diastereomeric salt formation process, was a matter of some difference of opinion. What appears to emerge is that there is no fixed likely duration for such a process and, indeed, no ability to predict with certainty whether one will be successful. The process may involve immediate success (most likely meaning days) or may be drawn out over weeks. Months or years would not be expected. The process may also be without success. The process involves trial and error and may

require perseverance. Yields may be obtained that are sufficient for analysis of the activity of an enantiomer.

(3) The formation of pharmaceutically acceptable salts of both racemates and enantiomers, including those in the form of an oil, was a common process prior to 1987, the techniques for which were known. There was a choice to be made in relation to which salt would be made, that process involving trial and error, and hence a choice in terms of acid. Hydrochloric and sulfuric acids were, however, common laboratory acids and were used to make pharmaceutical salts prior to 1987.

(4) (i) It was well understood prior to 1987 that enantiomers can exhibit different biological activity and toxicity. The thalidomide example had clearly provided a cautionary tale in this regard. It was not possible without separation and testing to predict with certainty the activity or toxicity of an enantiomer. Some prediction might be made based on knowledge of the intended receptor or the properties of salt of the relevant racemate, but that knowledge, where it was available, still could not ensure certainty.

(ii) There was and is a range of potential difference in activity between enantiomers. At the extremes, activity may be the same, or one enantiomer might have all the activity and the other none. Those two extremes were, however, less likely and would have been less expected than a result in the intermediate range. It was not unusual for one enantiomer to display most of the activity and the other little. The difference between the activity of the racemate and that of the active enantiomer could be expected to be about two-fold, though that difference might increase where the inactive enantiomer served to inhibit the activity of the active enantiomer when both were present in the racemate.

(iii) The toxicity of an enantiomer is not related to its physiological activity.

167 At [113], the primary judge stated, and it is not disputed, that the acids relevant to claims 2 to 5, that is, hydrochloric acid, sulphuric acid, hydrobromic acid and taurocholic acid, were all conventional for the preparation of salts.

The inventive step

168 The question is then whether the skilled worker in the art would have taken as a matter of routine the steps leading from the starting

point to the invention; whether, in applying common general knowledge, that person would have resolved the enantiomers of the racemate to obtain the d-enantiomer and obtained the claimed salts and pharmaceutical compositions and, for the purposes of claim 6, by the process there set out.

169 The primary judge stated at [110] that the result which might be described as "unexpected" in light of the French prior art patent was not so much the desirable characteristics of the d-enantiomer, for which the activity was in the expected broad range, but the inactivity of the l-enantiomer. His Honour considered that the claimed inventive step in relation to the product claim was the unexpected inactivity of the l-enantiomer. An unexpected result obtained in the course of investigation can, his Honour accepted, provide subject matter for an invention in appropriate circumstances.

170 His Honour said that it was common general knowledge as at the priority date that one enantiomer may have all of the activity and concluded that the discovery of the inactivity of the l-enantiomer was not so unexpected as to amount to an inventive step. In coming to this conclusion, the primary judge seems to have taken account of the information in the French prior art patent referred to in the specification of the Patent because Sanofi described the d-enantiomer as a selection from the prior published PCR 4099 and its enantiomers.

171 However, turning to the pharmaceutically acceptable salts of claims 2 to 5, his Honour said that, as the salts of the d-enantiomer were novel without any consideration as selection patents, the starting point for the assessment of obviousness was neither PCR 4099 nor the individual enantiomers, but rather, the common general knowledge. Since PCR 4099 did not form part of that common general knowledge, the primary judge concluded that the salts of its enantiomers were not obvious and represented an inventive step.

172 His Honour concluded that the claimed processes (claims 6 to 9), which described the liberation of the d-enantiomer from PCR 4099 by diastereomeric salt formation, were invalid for want of inventive step. In the context of assessing the obviousness of claim 6, the primary judge stated that the desire to obtain the d-enantiomer of PCR 4099 from the racemic mixture is taken for granted. That is, his Honour concluded that the starting point for the assessment of the obviousness of the process claims was the racemate, PCR 4099.

Consideration of the obviousness of particular claims of the Patent

Claims 1, 10 and 11 of the Patent

173 As noted above, the primary judge concluded that, for claim 1, the asserted inventive step related to the discovery of the inactivity of the l-enantiomer. In light of the common general knowledge, his Honour did not accept that this

discovery was so unexpected as to amount to an inventive step. That finding has not been shown to be in error. The idea to separate the enantiomers of PCR 4099 was not claimed to be part of the invention and indeed the person whose idea it was to do so was not named as an inventor ([21(12)]).

174 Claim 1 extends to the pharmaceutically acceptable salts of the d-enantiomer, undifferentiated. The finding of the primary judge, which is unchallenged in the appeal, is that the formation of pharmaceutically acceptable salts of enantiomers, including those in the form of an oil, was a common process prior to 1987, the techniques for which were known. It was obvious to prepare such salts to investigate biological activity. While his Honour also found that there was a choice to be made in terms of the particular acid, the person of ordinary skill armed with the racemate would know to make a salt that was pharmaceutically acceptable. There was no inventive step in the pharmaceutical carriers of claim 10 or the specific dose ranges of claim 11.

175 It follows that the invention as claimed in claims 1, 10 and 11 was obvious.

Claims 2 to 5 of the Patent

176 The conversion of the d-enantiomer to the salts claimed in claims 2 to 5 is described in the Patent as being carried out '*in a standard manner*'. As the primary judge noted at [111], the specification does not claim any inventive step in

the method of obtaining the salts once the d-enantiomer was known. The primary judge said that, if the starting point were the single enantiomer, he would have held that each salt claimed was obvious. This was because it was known that a pharmaceutically acceptable salt was useful for administration of an active compound, it was known how to prepare such salts using known mineral or organic acids, the acids chosen were conventional and standard methods of preparation were known (at 113]).

177 The primary judge's finding as to the choice of individual salts is unchallenged. That is, there was a choice to be made as to which salt to make, a process involving trial and error and a choice of acid. However, as his Honour said ([35(3)]), hydrochloric and sulphuric acids were common laboratory acids and were used to make pharmaceutical salts prior to 1987. The primary judge also said at [113], and it is not challenged, that all of the acids used to make the salts of claims 2 to 5 – hydrochloric acid, sulphuric acid, hydrobromic acid and taurocholic acid – were conventional. Trial and error are normal, every-day parts of laboratory work and non-inventive laboratory experiments. That is what the hypothetical skilled worker in a laboratory does – if the outcomes of experiments were known, there would be little point in doing them. That is the nature of everyday, non-inventive, research. A non-inventive worker in the field, looking to make a pharmaceutically acceptable salt of the d-enantiomer would, on the evidence, choose an acid, such as those readily available and commonly and conventionally used, and apply

common processes and techniques to make it. That was obvious, in the sense that the non-inventive skilled worker would have been directly led to those particular salts. There was no inventive step involved.

178 On this basis there is no difference whether the starting point is the racemic mixture or the single enantiomer. From the findings of the primary judge as to the steps that would have been taken as a matter of routine by the non-inventive worker in the relevant field to obtain an enantiomer or the salts of an enantiomer, it follows that the salts of claims 2 to 5, being the hydrochloride, the hydrogen sulphate, the hydrobromide and the taurocholate, were obvious and the claims to them did not involve an inventive step.

Claims 6 to 9 of the Patent

179 The process claim is not for the decision to obtain the enantiomer but to the means of doing so. Sanofi submits that more than routine experimentation was required and that diastereomeric salt formation was not the only method for obtaining enantiomers. It cites evidence in support. However, his Honour found that the method used to obtain the d-enantiomer was well-known in the field in Australia at the priority date as a classic means of obtaining enantiomers of a racemate mixture, which was applied to a known compound and produced the desired result. There were no circumstances, his

Honour held, to make the choice of this known process inventive.

180 The primary judge also held that each of the additional integers of claims 7, 8 and 9 was well-known in the field in Australia at the priority date and was available as part of the ordinary process of trial and error. The chiral resolving agent used was known, its use was not new and the solvent was well-known and commonly used. These findings of fact were open to his Honour on the evidence.

181 Accordingly, the primary judge held claims 6, 7, 8 and 9 obvious.

182 It has not been demonstrated that the primary judge was in error in finding claims 6 to 9 obvious.

MANNER OF MANUFACTURE

183 The primary judge said at [118] that, in his opinion, it could not be suggested that the subject matter of the claims of the Patent is outside the meaning of the expression "a manner of manufacture" as discussed in *National Research Development Corporation v Commissioner of Patents* (1959) 102 CLR 252. The claims are for compounds and processes in a field of useful pharmacological application. His Honour also expressed the view at [121] that it cannot be said that the Patent claims an invention that is not new on the face of the specification of the Patent without regard to what may be described as external evidence. In that context, his Honour applied the

relevant factors, as far as he discerned them, in *NV Philips Gloeilampenfabrieken v Mirabella International Pty Limited* (1995) 183 CLR 655 and *Advanced Building Systems Pty Limited v Ramset Fasteners (Aust) Pty Limited* (1998) 194 CLR 171 in the High Court and in *Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) 154 FCR 31 in the Full Court. His Honour did not accept that the French specification was incorporated by reference as a whole and for all purposes into the specification in suit but only sufficiently to understand the reference to the racemic compound in the specification in suit. Even if the French specification were incorporated as a whole, his Honour said it would take the matter no further than his decision on novelty. Spirit says that this aspect of his Honour's reasoning is an acceptance that, if the French prior art patent were incorporated by reference as a whole, his Honour accepted that at least claims 1, 10 and 11 would be invalid on the ground that they did not define a manner of manufacture.

184 Apotex's submission that the claims of the Patent do not define a manner of manufacture is based on the effect of the reference to the French prior art patent which, it submits, is then incorporated by reference. As a result, Apotex says, there is no invention which is new or inventive on the face of the specification of the Patent.

185 The French prior art patent discloses PCR 4099, the racemic mixture from which the d-enantiomer the subject of the claims of the Patent is obtained. It is also in the French prior

art patent that the activity of platelet aggregation inhibition is disclosed. Apotex says that the French prior art patent:

- Discloses both enantiomers, as well as the racemic mixture – indeed, it claims them as part of the invention;
- Discloses the particular salts of those enantiomers which are the subject of the claims in the Patent, and claims them as part of the invention;
- Discloses the therapeutic effect of the enantiomers, in inhibiting blood-platelet aggregation and thrombosis;
- Discloses that the derivatives (including the enantiomers) are well-tolerated, exhibit low toxicity and are useful; and
- Discloses and claims pharmaceutical ('*therapeutic*') compositions containing them.

186 Apotex and Spirit submit that the primary judge erred in failing to find that the specification of the French prior art patent (the French patent application referred to in the Patent was granted without amendment as the French prior art patent) was incorporated by reference for the purposes of considering the question of whether the claims of the Patent involved a manner of new manufacture on the face of the specification.

187 Apotex then points to the fact that the specification of the Patent says that the salts of the d-enantiomer were prepared in a standard manner, as the primary judge accepted.

188 Apotex submits that it follows from the disclosures in the French prior art patent and in the specification that there is no "new" or "inventive" invention on the face of the specification and that the product claims (claims 1, 2 to 5, 10 and 11) do not define a manner of new manufacture.

189 The submissions of Apotex and Spirit seem to assume that, if the French prior art patent were wholly incorporated by reference, it follows that there is no manner of new manufacture demonstrated in the specification of the Patent, This seems to be because the French prior art patent discloses derivative No 1, the racemic mixture PCR 4099 and its preparation, together with the disclosure and claim to the enantiomers of, *inter alia*, that compound. Apotex and Spirit then rely on admissions in the specification of the Patent and findings of the primary judge that the method of preparation of the d-enantiomer was routine, as were the methods of salt formation. Spirit also makes reference to the fact that the primary judge found that, '[o]*n any view*', derivative No 1, the first example in the French prior art patent, was expressly disclosed as one of the most promising of the compounds described in and exemplified in that patent.

190 The specification of the Patent acknowledges that the racemic mixture corresponding to the formula of the compound of the invention, which formula encompasses the racemic mixture and the d- and l-enantiomers, was described in the French prior art patent. The specification also states that, in an unexpected manner, of the two

enantiomers, only the d-enantiomer exhibits platelet aggregation inhibiting activity and, moreover, the inactive l-enantiomer is less well-tolerated. It is for that reason, impliedly, that the patentee continued to develop the addition salts of the d-enantiomer and pharmaceutical compositions. The description in the specification concludes with the statement that, on account of *'its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders'*.

191 The French prior art patent also reported the activity of the derivatives and their inhibiting activity on platelet aggregation and anti-thrombotic action as well as toxicological and pharmacological data that demonstrated the low toxicity of the compounds. While the enantiomers were disclosed and claimed, no distinction was drawn between the activity and toxicity of those enantiomers or between the enantiomers and the racemate. That awaited the work set out in the Patent. The results were described as *'unexpected'* and led to the claims directed to one of the enantiomers and the demonstration that the other enantiomer was not active.

192 Accepting that the French prior art patent was incorporated wholly into the Patent for the purpose of assessing whether, on its face, the Patent disclosed a manner of manufacture, in our opinion it cannot be said that the Patent failed to do so. It is not apparent from the face of the

specification that the necessary quality of inventiveness is absent.

CONCLUSION

193 It follows that:

- In respect of claim 1, to the extent that the claim is to the d-enantiomer, claim 1 is invalid on the ground of lack of novelty but, to the extent that the claim is to the pharmaceutically acceptable salts of the d-enantiomer, claim 1 is novel.
- The subject matter of claims 2 to 5 are novel.
- The subject matter of claims 10 and 11 are invalid on the ground of lack of novelty.
- The subject matter of claims 1, 2 to 5, 6 to 9, 10 and 11 are invalid on the ground of lack of inventive step.
- The subject matter of claims 1, 2 to 5, 10 and 11 do define a manner of manufacture.

194 The parties have asked that the question of costs be deferred until after the Court has published its reasons. The parties should submit proposed orders to give effect to these reasons and considerations, including any directions necessary for the resolution of any question of costs.

I certify that the preceding one hundred and fifty-four (154) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justices Bennett and Middleton.

Associate: /s/

Dated: 29 September 2009

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